(1390 REV. 5-93) US DEPT. OF COMMERCE PATENT & TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER
103514

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

U.S. APPLICATION NO. (if known, sec 37 C.F.R.1.5)
09/319156

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FR98/01460	July 7, 1998	July 7, 1997

512 Rec'd PCT/PTO 02 JUN 1999

TITLE OF INVENTION
RETROVIRAL NUCLEIC MATERIAL AND NUCLEOTIDE FRAGMENTS, IN PARTICULAR ASSOCIATED WITH MULTIPLE SCLEROSIS AND/OR RHEUMATOID ARTHRITIS, FOR DIAGNOSTIC, PROPHYLACTIC AND THERAPEUTIC USES

APPLICANT(S) FOR DO/EO/US
Glaucia PARAHNOS-BACCALA, Florence KOMURIAN-PRADEL, Frederic BEDIN, Mireille SODOYER, Catherine OTT, Francois MALLET, Herve PERRON and Bernard MANDRAND

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. ☐ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)

6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.

8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.

    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☐ A small entity statement.

16. ☐ Other items or information:

PCT/PTO 2 JUN 1999

U.S. APPLICATION NO. (if known, see 37 C.F.R. 1.5) 09/319156	INTERNATIONAL APPLICATION NO. PCT/FR98/01460	ATTORNEY'S DOCKET NUMBER 103514

17. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National fee (37 CFR 1.492(a)(1)-(5)):		
Search Report has been prepared by the EPO or JPO.....$840.00	$840.00	
International preliminary examination fee paid to USPTO (37 CFR1.482).....$670.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)).....$760.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....$970.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....$ 96.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$840.00	
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

Claims	Number Filed	Number Extra	Rate		
Total Claims	26- 20 =	---	X $ 18.00	$108.00	
Independent Claims	14- 3 =	---	X $ 78.00	$858.00	
Multiple dependent claim(s)(if applicable)			+ $260.00	$	
TOTAL OF ABOVE CALCULATIONS =				$1,806.00	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28). -				$----	
SUBTOTAL =				$1,806.00	
Processing fee of $130.00 for furnishing the English translation later than ☐ 20 ☐ 30 month from the earliest claimed priority date (37 CFR 1.492(f)). +				$---	
TOTAL NATIONAL FEE =				$1,806.00	
				Amount to be refunded	$
				Charged	$

a. ☒ Check No. 100859 in the amount of $1,806.00 to cover the above fees is enclosed.
b. ☐ Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.
c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 15-0461. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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(1390 Rev.8-93)

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Glaucia PARAHNOS-BACCALA, Florence KOMURIAN-PRADEL, Frederic BEDIN, Mireille SODOYER, Catherine OTT, Francois MALLET, Herve PERRON and Bernard MANDRAND

Application No.: U.S. National Stage of PCT/FR98/01460

Filed: June 2, 1999 Docket No.: 103514

For: RETROVIRAL NUCLEIC MATERIAL AND NUCLEOTIDE FRAGMENTS, IN PARTICULAR ASSOCIATED WITH MULTIPLE SCLEROSIS AND/OR RHEUMATOID ARTHRITIS, FOR DIAGNOSTIC, PROPHYLACTIC AND THERAPEUTIC USES

PRELIMINARY AMENDMENT

Assistant Commissioner of Patents
Washington, D. C. 20231

Sir:

Prior to initial examination, please amend the above-identified application as follows:

IN THE CLAIMS:

Please amend claims 8, 13, 18, 20, 22, 23, 25 and 26 as follows:

Claim 8, line 4, delete "at nucleotide [sic]".

Claim 13, lines 1-2, change "any one of the preceding claims" to --claim 3--.

Claim 18, line 5, change "any one of claims 14 to 17" to --claim 14--.

Claim 20, line 7, change "any one of claims 8 to 11" to --claim 8--.

Claim 22, lines 3-5, change "any one of claims 1 to 7 or a fragment according to any one of claims 14 to 17" to --claim 1--.

Claim 23, lines 2-3, change "any one of claims 14 to 17" to --claim 14--.

Claim 25, lines 5-6, change "any one of claims 14 to 17" to --claim 14--.

Claim 26, lines 7-8, change "any one of claims 14 to 17" to --claim 14--.

REMARKS

Claims 1-26 are pending. By this Preliminary Amendment, claim 8 is amended to eliminate unnecessary language and claims 13, 18, 20, 22, 23, 25 and 26 are amended to eliminate multiple dependency. Prompt and favorable examination is respectfully requested.

Respectfully submitted,

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RETROVIRAL NUCLEIC MATERIAL AND NUCLEOTIDE FRAGMENTS, IN PARTICULAR ASSOCIATED WITH MULTIPLE SCLEROSIS AND/OR RHEUMATOID ARTHRITIS, FOR DIAGNOSTIC, PROPHYLACTIC AND THERAPEUTIC USES

Multiple sclerosis (MS) is a demyelinizing disease of the central nervous system (CNS) of which the complete cause still remains unknown.

Numerous studies have supported the hypothesis for a viral etiology of the disease, but none of the known viruses tested has proved to be the causative agent tested for: a review of the viruses tested for in MS for many years has been carried out by E. Norrby and R.T. Johnson.

Recently, a retrovirus, different from the known human retroviruses, was isolated from patients suffering from MS. The authors were able to show that this retrovirus could be transmitted in vitro, that patients suffering from MS produced antibodies capable of recognizing proteins associated with the infection of the leptomeningeal cells by this retrovirus, and that the expression of the latter could be greatly stimulated by the immediate-early genes of some herpesviruses.

All these results argue in favor of the role in MS of at least one unknown retrovirus or of a virus having a reverse transcriptase (RT) activity which is detectable by the method published by H. Perron and termed "LM7-type RT" activity.

The studies by the applicant have made it possible to obtain two continuous cell lines infected with natural isolates obtained from two different patients suffering from MS, by a culture method as described in the document WO-A-93 20188, whose content is incorporated by reference into the present description. These two lines derived from cells of human choroid plexus, called LM7PC and PLI-2, were deposited at the E.C.A.C.C. on 22 July 1992 and 8 January 1993, respectively, under numbers 92 072201

and 93 010817, in accordance with the provisions of the Treaty of Budapest. Moreover, the viral isolates possessing an LM7-type RT activity have also been deposited at the E.C.A.C.C. under the overall name of "strains". The "strain" or isolate harbored by the PLI-2 line, called POL-2, was deposited at the E.C.A.C.C. on 22 July 1992 under No. V92072202. The "strain" or isolate harbored by the LM7PC line, called MS7PG, was deposited at the E.C.A.C.C. on 8 January 1993 under No. V93010816.

Using the abovementioned cultures and isolates, characterized by biological and morphological criteria, efforts were then made to characterize the genetic material associated with the viral particles produced in these cultures.

The proportions of genome already characterized were used to develop molecular detection tests for the viral genome and immunoserological tests, using the amino acid sequences encoded by the nucleotide sequences of the viral genome, in order to detect the immune response directed against epitopes associated with the viral infection and/or expression.

These tools have already made it possible to confirm an association between MS and the expression of the sequences identified in the patents cited further on. However, the viral system discovered by the applicant is related to a complex retroviral system. Indeed, the sequences which are found to be encapsidated in the extracellular viral particles produced by the different cultures of cells of patients suffering from MS show clearly that there is co-encapsidation of retroviral genomes which are related but different from the "wild-type" retroviral genome which produces the infectious viral particles. This phenomenon was observed between replicative retroviruses and endogenous retroviruses belonging to the same family, or even heterologous retroviruses. The concept of endogenous retrovirus is very important in the context of our discovery because, in the case of

MSRV-1, it has been observed that endogenous retroviral sequences comprising sequences homologous to the MSRV-1 genome exist in normal human DNA. The existence of endogenous retroviral elements (ERV) related to MSRV-1 through all or part of their genome explains the fact that the expression of the MSRV-1 retrovirus in human cells can interact with related endogenous sequences. These interactions are found in the case of pathogenic and/or infectious endogenous retroviruses (for example some ecotropic strains of the Murine Leukemia virus), in the case of exogenous retroviruses whose nucleotide sequence may be found partially or completely in the form of ERVs, in the genome of the host animal (e.g. mouse mammary tumor exogenous virus transmitted via milk). These interactions consist mainly of (i) a transactivation or co-activation of ERVs by the replicative retrovirus, (ii) an "illegitimate" encapsidation of related RNAs of ERVs, or of ERVs - or even of cellular RNAs - simply possessing compatible encapsidation sequences, into the retroviral particles produced by the expression of the replicative strain, which are sometimes transmissible and sometimes with an inherent pathogenicity, and (iii) relatively high recombinations between the co-encapsidated genomes, in particular in the reverse transcription phases, which lead to the formation of hybrid genomes, which are sometimes transmissible and sometimes with an inherent pathogenicity.

Thus, (i) various MSRV-1-related sequences have been found in purified viral particles; (ii) molecular analysis of the various regions of the MSRV-1 retroviral genome should be carried out by systematically analyzing the co-encapsidated, interfering and/or recombinant sequences which are generated by the infection and/or expression of MSRV-1; furthermore, some clones may have portions of defective sequences produced by the retroviral replication and the template and/or transcription errors caused by reverse transcriptase; (iii) the families of sequences

related to the same retroviral genomic region are the supports for an overall diagnostic detection which may be optimized by the identification of invariable regions among the clones expressed and by the identification of reading frames responsible for the production of antigenic and/or pathogenic polypeptides which may only be produced by a portion, or even only one, of the clones expressed and under these conditions, the systematic analysis of the clones expressed in one region of a given gene makes it possible to evaluate the frequency of variation and/or recombination of the MSRV-1 genome in this region and to define the optimum sequences for the applications, in particular the diagnostic applications; (iv) the pathology caused by a retrovirus such as MRSV-1 may be a direct effect of its expression and of the proteins or peptides produced as a result, but also an effect of the activation, encapsidation, recombination of related or heterologous genomes and proteins or peptides produced as a result; thus, these genomes associated with the expression and/or infection by MSRV-1 are an integral part of the potential pathogenicity of this virus and therefore constitute diagnostic detection supports and particular therapeutic targets. Likewise, any agent which is associated with, or which is a cofactor for these interactions responsible for the pathogenicity in question, such as MSRV-2 or the gliotoxic factor described in the patent application published under the No. FR-2,716,198, can participate in the development of an overall and very effective strategy for therapeutic diagnosis, prognosis, monitoring and/or integrated therapy for MS in particular, but also for any other disease associated with the same agents.

In this context, a parallel discovery has been made in another autoimmune disease, rheumatoid arthritis (RA), which has been described in the French patent application filed under the No. 95 02960. This discovery shows that, by applying methodological

approaches similar to those which were used in the studies by the applicant on MS, it has been possible to identify a retrovirus expressed in RA which shares the sequences described for MSRV-1 in MS and also the co-existence of an MSRV-2-associated sequence which is also described in MS. As regards MSRV-1, the sequences commonly detected in MS and RA relate to the *pol* and *gag* genes. On the basis of current knowledge, it is possible to combine the *gag* and *pol* sequences described with the MSRV-1 strains expressed in these two diseases.

The present patent application has as its object various results, supplementary in relation to those already protected by the French patent applications:

- No. 92/04322 of 03.04.1992, published under No. 2,689,519;
- No. 92/13447 of 03.11.1992, published under No. 2,689,521;
- No. 92/13443 of 03.11.1992, published under No. 2,689,520;
- No. 94/01529 of 04.02.1994, published under No. 2,715,936;
- No. 94/01531 of 04.02.1994, published under No. 2,715,939;
- No. 94/01530 of 04.02.1994, published under No. 2,715,936;
- No. 94/01532 of 04.02.1994, published under No. 2,715,937;
- No. 94/14322 of 24.11.1994, published under No. 2,727,428;
- No. 94/15810 of 23.12.1994, published under No. 2,728,585;

and

- Patent Application WO 97/06260.

The present invention relates, first of all, to a nucleic material, which may consist of a retroviral material, in isolated or purified state, which may be understood or characterized in various ways:

- it comprises a nucleotide sequence chosen from the group which consists of (i) the sequences SEQ ID NO: 112, SEQ ID NO: 114, SEQ ID NO: 117, SEQ ID NO: 120, SEQ ID NO: 124, SEQ ID NO: 130, SEQ ID NO: 141 and SEQ ID NO: 142; (ii) the sequences complementary to sequences (i); and (iii) the sequences equivalent to sequences (i) or (ii), in particular the sequences having, for every series of 100 contiguous monomers, at least 50%, and preferentially at least 70% homology with sequences (i) or (ii) respectively;

- it encodes a polypeptide having, for every contiguous series of at least 30 amino acids, at least 50%, and preferably at least 70% homology with a peptide sequence chosen from the group which consists of SEQ ID NO: 113, SEQ ID NO: 115, SEQ ID NO: 118, SEQ ID NO: 121, SEQ ID NO: 135 and SEQ ID NO: 137;

- its pol gene comprises a nucleotide sequence identical or equivalent to a sequence chosen from the group which consists of SEQ ID NO: 112, SEQ ID NO: 124 and their complementary sequences;

- the 5' end of its pol gene starts at nucleotide 1419 of SEQ ID NO: 130;

- its pol gene encodes a polypeptide having, for every contiguous series of at least 30 amino acids, at least 50%, and preferably at least 70% homology with the peptide sequence SEQ ID NO: 113;

- the 3' end of its gag gene ends at nucleotide 1418 of SEQ ID NO: 130;

- its env gene comprises a nucleotide sequence identical or equivalent to a sequence chosen from the group which consists of SEQ ID NO: 117, and its complementary sequences;

- its env gene comprises a nucleotide sequence which starts at nucleotide 1 of SEQ ID NO: 117 and ends at nucleotide at nucleotide [sic] 233 of SEQ ID NO: 114;

- its env gene encodes a polypeptide having, for every contiguous series of at least 30 amino acids,

at least 50%, and preferably at least 70% homology with the sequence SEQ ID NO: 118;

- the U3R region of its 3' LTR comprises a nucleotide sequence which ends at nucleotide 617 of SEQ ID NO: 114;

- the RU5 region of its 5' LTR comprises a nucleotide sequence which starts at nucleotide 755 of SEQ ID NO: 120 and ends at nucleotide 337 of SEQ ID NO: 141 or SEQ ID NO: 142;

- a retroviral nucleic material comprising a sequence which starts at nucleotide 755 of SEQ ID NO: 120 and which ends at nucleotide 617 of SEQ ID NO: 114;

- the retroviral nucleic material as defined above is in particular associated with at least one autoimmune disease such as multiple sclerosis or rheumatoid arthritis.

The invention also relates to a nucleotide fragment which corresponds to at least one of the following definitions:

- it comprises or consists of a nucleotide sequence chosen from the group which consists of (i) the sequences SEQ ID NO: 112, SEQ ID NO: 114, SEQ ID NO: 117, SEQ ID NO: 120, SEQ ID NO: 124, SEQ ID NO: 130, SEQ ID NO: 141 and SEQ ID NO: 142; (ii) the sequences complementary to sequences (i); and (iii) the sequences equivalent to sequences (i) or (ii), in particular the sequences having, for every series of 100 contiguous monomers, at least 50%, and preferentially at least 70% homology with sequences (i) or (ii) respectively;

- it comprises or consists of a nucleotide sequence encoding a polypeptide having, for every contiguous series of at least 30 amino acids, at least 50%, and preferably at least 70% homology with a peptide sequence chosen from the group which consists of SEQ ID NO: 113, SEQ ID NO: 115, SEQ ID NO: 118, SEQ ID NO: 121, SEQ ID NO: 135 and SEQ ID NO: 137.

Other subjects of the present invention are the following:

- a nucleic probe for the detection of a retrovirus associated with multiple sclerosis and/or rheumatoid arthritis, capable of hybridizing specifically with any fragment defined above and belonging to the genome of said retrovirus; it advantageously possesses from 10 to 100 nucleotides, preferably from 10 to 30 nucleotides;

- a primer for the amplification, by polymerization, of an RNA or of a DNA of a retrovirus associated with multiple sclerosis and/or rheumatoid arthritis, which comprises a nucleotide sequence identical or equivalent to at least a portion of the nucleotide sequence of a fragment defined above, in particular a nucleotide sequence having, for every series of 10 contiguous monomers, at least 50%, preferably at least 70% homology with at least said portion of said fragment; preferably the nucleotide sequence of a primer of the invention is chosen from SEQ ID NO: 116, SEQ ID NO: 119, SEQ ID NO: 122, SEQ ID NO: 123, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, SEQ ID NO: 132, and SEQ ID NO: 133;

- an RNA or a DNA, and in particular a replication and/or expression vector, comprising a genomic fragment of the nucleic material or a fragment defined above;

- a peptide encoded by any open reading frame belonging to a nucleotide fragment defined above, in particular a polypeptide, for example oligopeptide forming or comprising an antigenic determinant recognized by sera of patients infected with the MSRV-1 virus, and/or in whom the MSRV-1 virus has been reactivated; a preferential peptide comprises a sequence identical, partially or completely, or equivalent to a sequence chosen from SEQ ID NO: 113, SEQ ID NO: 115, SEQ ID NO: 118, SEQ ID NO: 121, SEQ ID NO: 135 and SEQ ID NO: 137;

- a diagnostic, prophylactic or therapeutic composition, in particular for inhibiting the

expression of at least one retrovirus associated with multiple sclerosis and/or rheumatoid arthritis, comprising a nucleotide fragment defined above;

- a method for detecting a retrovirus associated with multiple sclerosis and/or rheumatoid arthritis, in a biological sample, comprising the steps consisting of bringing an RNA and/or a DNA assumed to belong to or obtained from said retrovirus, or their complementary RNA and/or DNA, into contact with a composition comprising a nucleotide fragment defined above.

Before detailing the invention, various terms used in the description and the claims are now defined:

- strain or isolate is understood to mean any infectious and/or pathogenic biological fraction containing, for example, viruses and/or bacteria and/or parasites, generating a pathogenic and/or antigenic power, harbored by a culture or a live host; by way of example, a viral strain according to the preceding definition may contain a co-infectious agent, for example a pathogenic protist,

- the term "MSRV" used in the present description designates any pathogenic and/or infectious agent, as associated with MS, in particular a viral species, the attenuated strains of said viral species, or the interfering defective particles or particles containing co-encapsidated genomes or alternatively genomes recombined with a portion of the MSRV-1 genome, which are derived from this species. It is known that viruses and particularly viruses containing RNA exhibit variability, following in particular relatively high rates of spontaneous mutation, which will be taken into account below to define the concept of equivalence,

- human virus is understood to mean a virus capable of infecting or of being harbored by human beings,

- given all the natural or induced variations and/or recombination which may be encountered in practice in the present invention, the objects thereof,

defined above and in the claims, have been expressed by comprising the equivalents or derivatives of the various biological materials defined below, in particular homologous nucleotide or peptide sequences,

- the variant of a virus or of a pathogenic and/or infectious agent according to the invention comprises at least one antigen recognized by at least one antibody directed against at least one corresponding antigen of said virus and/or of said pathogenic and/or infectious agent, and/or a genome in which any portion is detected by at least one hybridization probe, and/or at least one nucleotide amplification primer specific for said virus and/or pathogenic and/or infectious agent, under defined hybridization conditions well known to persons skilled in the art,

- according to the invention, a nucleotide fragment or an oligonucleotide or a polynucleotide is a stretch of monomers, or a biopolymer, characterized by the informational sequence of the natural nucleic acids, which is capable of hybridizing to any other nucleotide fragment under predefined conditions, it being possible for the stretch to contain monomers of different chemical structures and to be obtained from a natural nucleic acid molecule and/or by genetic recombination and/or by chemical synthesis; a nucleotide fragment may be identical to a genomic fragment of the MSRV-1 virus considered by the present invention, in particular a gene of the latter, for example pol or env in the case of said virus;

- thus, a monomer may be a natural nucleic acid nucleotide in which the constituent components are a sugar, a phosphate group and a nitrogen base; in RNA, the sugar is ribose; in DNA, the sugar is 2-deoxy-ribose; depending on whether DNA or RNA is involved, the nitrogen base is chosen from adenine, guanine, uracil, cytosine, thymine; or the nucleotide may be modified in at least one of the three constituent components; by way of example, the modification may

occur at the level of the bases, generating modified bases such as inosine, 5-methyl-deoxycytidine, deoxyuridine, 5-dimethylamineodeoxyuridine [sic], 2,6-diamineopurine [sic], 5-bromodeoxyuridine and any other modified base promoting hybridization; at the level of the sugar, the modification may consist in the replacement of at least one deoxyribose with a polyamide, and at the level of the phosphate group, the modification may consist in its replacement with esters, in particular chosen from the esters of diphosphate, of alkyl and arylphosphonate and of phosphorothioate,

- "informational sequence" is understood to mean any ordered series of monomers, whose chemical nature and in which the order in a reference direction, constitute or otherwise a functional information of the same quality as that for the natural nucleic acids,

- hybridization is understood to mean the process during which, under appropriate operating conditions, two nucleotide fragments, having sufficiently complementary sequences, become annealed to form a complex, in particular a double or triple, structure, preferably in helical form,

- a probe comprises a nucleotide fragment synthesized by the chemical route or obtained by digestion or enzymatic cleavage of a longer nucleotide fragment, comprising at least six monomers, advantageously from 10 to 100 monomers, preferably 10 to 30 monomers, and possessing a hybridization specificity under defined conditions; preferably, a probe possessing less than 10 monomers is not used alone, but is used in the presence of other probes which are equally short in length or otherwise; under certain specific conditions, it may be useful to use probes which are greater than 100 monomers in size; a probe may be used in particular for diagnostic purposes, and it may be, for example, capture and/or detection probes,

- the capture probe may be immobilized on a solid support by any appropriate means, that is to say directly or indirectly, for example by covalent bonding or passive adsorption,

- the detection probe may be labeled by means of a marker chosen in particular from radioactive isotopes, enzymes chosen in particular from peroxidase and alkaline phosphatase and those capable of hydrolyzing a chromogenic, fluorigenic or luminescent substrate, chromophoric chemical compounds, chromogenic, fluorigenic or luminescent compounds, analogs of nucleotide bases, and biotin,

- the probes used for diagnostic purposes of the invention may be used in all known hybridization techniques, and in particular the so-called "DOT-BLOT" technique, "SOUTHERN BLOT" technique, "NORTHERN BLOT" technique which is a technique identical to the "SOUTHERN BLOT" technique but which uses RNA as target, the SANDWICH technique; advantagously, the SANDWICH technique is used in the present invention, comprising a specific capture probe and/or a specific detection probe, it being understood that the capture probe and the detection probe must have a nucleotide sequence which is at least partially different,

- any probe according to the present invention may hybridize in vivo or in vitro with the RNA and/or with the DNA, in order to block the replication, in particular translation and/or transcription, phenomena and/or to degrade said DNA and/or RNA,

- a primer is a probe comprising at least six monomers, and advantageously from 10 to 30 monomers, possessing hybridization specificity under defined conditions, for the initiation of an enzymatic polymerization, for example in an amplification technique such as PCR (Polymerase Chain Reaction), in an extension method such as sequencing, in a reverse transcription method and the like,

- two nucleotide or peptide sequences are said to be equivalent or derived with respect to each other,

or with respect to a reference sequence, if functionally the corresponding biopolymers can play substantially the same role, without being identical, in relation to the application or use considered, or in the technique in which they are involved; particularly equivalent are two sequences obtained because of the natural variability, in particular spontaneous mutation, of the species from which they were identified, or induced mutation, as well as two homologous sequences, the homology being defined below,

- "variability" is understood to mean any spontaneous or induced modification of a sequence, in particular by substitution, and/or insertion, and/or deletion of nucleotides and/or of nucleotide fragments, and/or extension and/or shortening of the sequence at least at one of the ends; a nonnatural variability may result from the genetic engineering techniques used, for example from the choice of the degenerate or nondegenerate synthetic primers selected to amplify a nucleic acid; this variability may result in modifications of any starting sequence, considered as a reference, and which may be expressed by a degree of homology with respect to said reference sequence,

- homology characterizes the degree of identity of two compared nucleotide or peptide fragments; it is measured by the percentage identity which is in particular determined by direct comparison of nucleotide or peptide sequences, with respect to reference nucleotide or peptide sequences,

- any nucleotide fragment is said to be equivalent to or derived from a reference fragment if it has a nucleotide sequence equivalent to the sequence of the reference fragment; according to the preceding definition, in particular equivalent to a reference nucleotide fragment are:

(a) any fragment capable of hybridizing, at least partially, with the complementary to the reference fragment,

(b) any fragment whose alignment with the reference fragment leads to the identification of identical contiguous bases, in a greater number than with any other fragment obtained from another taxonomic group,

(c) any fragment resulting or capable of resulting from the natural variability of the species from which it is obtained,

(d) any fragment which may result from genetic engineering techniques applied to the reference fragment,

(e) any fragment, containing at least eight contiguous nucleotides, encoding a peptide homologous or identical to the peptide encoded by the reference fragment,

(f) any fragment different from the reference fragment through insertion, deletion, substitution of at least one monomer, extension, or shortening at least at one of its ends; for example, any fragment corresponding to the reference fragment, flanked at least at one of its ends by a nucleotide sequence not encoding a polypeptide,

- polypeptide is understood to mean in particular any peptide of at least two amino acids, in particular oligopeptide, protein, extracted, separated, or substantially isolated or synthesized, through the involvement of humans, in particular those obtained by chemical synthesis, or through expression in a recombinant organism,

- polypeptide partially encoded by a nucleotide fragment is understood to mean a polypeptide having at least three amino acids encoded by at least nine contiguous monomers included in said nucleotide fragment,

- an amino acid is said to be analogous to another amino acid when their respective physicochemical characteristics, such as polarity, hydrophobicity and/or basicity, and/or acidity, and/or

neutrality, are substantially the same; thus, a leucine is analogous to an isoleucine,

- any polypeptide is said to be equivalent to or derived from a reference polypeptide if the polypeptides compared have substantially the same properties, and in particular the same antigenic, immunological, enzymatic and/or molecular recognition properties; in particular equivalent to a reference polypeptide is:

(a) any polypeptide possessing a sequence in which at least one amino acid has been replaced by an analogous amino acid,

(b) any polypeptide having an equivalent peptide sequence, obtained by natural or induced variation of said reference polypeptide, and/or of the nucleotide fragment encoding said polypeptide,

(c) a mimotope of said reference polypeptide,

(d) any polypeptide from whose sequence one or more amino acids of the L series are replaced by an amino acid of the D series, and vice versa,

(e) any polypeptide into whose sequence a modification of the side chains of the amino acids has been introduced, such as for example an acetylation of the amine-containing functions, a carboxylation of the thiol functions, an esterification of the carboxyl functions,

(f) any polypeptide in whose sequence one or more peptide bonds have been modified, such as for example the carba, retro, inverso, retro-inverso, reduced, and methylene-oxy bonds,

(g) any polypeptide in which at least one antigen is recognized by an antibody directed against a reference polypeptide,

- the percentage identity characterizing the homology between two peptide fragments compared is according to the present invention at least 50% and preferably at least 70%.

Given that a virus possessing a reverse transcriptase enzymatic activity may be genetically

characterized both in RNA and DNA form, both the viral DNA and RNA will be mentioned in order to characterize the sequences relative to a virus possessing such a reverse transcriptase activity, termed MSRV-1 according to the present description.

The expressions of order which are used in the present description and the claims, such as "first nucleotide sequence", are not selected to express a particular order, but to define the invention more clearly.

Detection of a substance or agent is understood below to mean an identification, a quantification or a separation or isolation of said substance or of said agent.

The invention will be understood more clearly on reading the detailed description which follows which is made with reference to the appended figures in which:

Figure 1 represents the general structure of the proviral DNA and the genomic RNA of MSRV-1.

Figure 2 represents the nucleotide sequence of the clone called CL6-5' (SEQ ID NO: 112) and three potential reading frames in amino acids presented under the nucleotide sequence.

Figure 3 represents the nucleotide sequence of the clone called CL6-3' (SEQ ID NO: 114) and three potential reading frames in amino acids presented under the nucleotide sequence.

Figure 4 represents the nucleotide sequence of the clone called C15 (SEQ ID NO: 117) and three potential reading frames in amino acids presented under the nucleotide sequence.

Figure 5 represents the nucleotide sequence of the clone called 5M6 (SEQ ID NO: 120) and three potential reading frames in amino acids presented under the nucleotide sequence.

Figure 6 represents the nucleotide sequence of the clone called CL2 (SEQ ID NO: 130) and three

potential reading frames in amino acids presented under the nucleotide sequence.

Figure 7 represents three potential reading frames in amino acids expressed by pET28C-clone 2 and presented under the nucleotide sequence.

Figure 8 represents three potential reading frames in amino acids expressed by pET21C-clone 2 and presented under the nucleotide sequence.

Figure 9 represents the nucleotide sequence of the clone called LB13 (SEQ ID NO: 141) and three potential reading frames in amino acids presented under the nucleotide sequence.

Figure 10 represents the nucleotide sequence of the clone called LA15 (SEQ ID NO: 142) and three potential reading frames in amino acids presented under the nucleotide sequence.

Figure 11 represents the nucleotide sequence of the clone called LB16 (SEQ ID NO: 124) and three potential reading frames in amino acids presented under the nucleotide sequence.

Figure 12 represents the promoter activity expressed in cpm/4 min of the U3R sequences subcloned from LTRs of different origins into the plasmid PCAT3. PCAT3 means plasmid alone, PCAT-PH74 means plasmid plus endogenous U3R clone expressed in the placenta, PCAT-c16 means plasmid plus U3R clone amplified in the RNA of an MS plasma, PCAT-5M6 means plasmid plus U3R region amplified in the cellular DNA, "no plasmid" means absence of plasmid in the test.

Figure 13 represents the MSRV1 env and 3' LTR sequences. The horizontal arrows indicate the start of the env, U3 and R regions. In the env region, the signal peptide and the potential immunosuppressive region are underlined, the potential glycosilation sites are boxed and the potential cleavage sites are indicated by vertical arrows. In the U3R region: the regulatory element CAAT and the TATA Box are underlined, the "cap" site and the polyadenylation signal are also indicated.

Figure 14 represents the 5' LTR (RU5) region followed by a PBS site (primer binding site) complementary to the Trp tRNA and by a gag gene encoding a protein of about 487 amino acids. The amino acids conserved in the nucleocapsid are underlined twice. The amino acids defining the region of greatest homology in the capsid are in bold and underlined once. The / symbols in the amino acid sequence indicate variations observed depending on the clones and, in the nucleotide sequence, they indicate frame jumps in some clones. The boxed regions correspond to epitopes identified by peptide analysis of the C-terminal region.

Figure 15 represents the integrase region of MSRV1, the nucleotide sequence and the amino acid sequence deduced from the integrase region corresponding to clone 87-23. In Figure 15, // means a frame jump which has been suppressed in order to restore the potential ORF. The letters in underlined bold characters represent the conserved amino acids in the retroviral integrases.

Figure 16 describes the nucleotide and peptide sequences of clone B13 (identical to clone FBd13 described in previous applications) with indication of the ORFs and stop codons represented by a dot. The underlined region in bold represents the potential immunosuppressive domain. The single underlined domain represents the start of the 3' LTR.

EXAMPLE 1: PREPARATION OF A CL6-5' REGION ENCODING THE N-TERMINAL END OF INTEGRASE AND OF A CL6-3' REGION CONTAINING THE 3' TERMINAL SEQUENCE OF THE MSRV-1 GENOME

A 3' RACE was carried out on the total RNA extracted from plasma from a patient suffering from MS. A healthy control plasma, treated under the same conditions, was used as negative control. The synthesis of cDNA was carried out with an oligo dT primer identified by SEQ ID NO: 68 (5' GAC TCG CTG CAG ATC GAT

TTT TTT TTT TTT TTT T 3') and the reverse transcriptase "Expand™ RT" from Boehringer according to the conditions recommended by the company. A PCR was carried out with the enzyme Klentaq (Clontech) under the following conditions: 94°C 5 min then 93°C 1 min, 58°C 1 min, 68°C 3 min over 40 cycles and 68°C for 8 min, with a final reaction volume of 50 µl.

Primers used for the PCR:

- 5' primer, identified by SEQ ID NO: 69

5' GCC ATC AAG CCA CCC AAG AAC TCT TAA CTT 3';

- 3' primer, identified by SEQ ID NO: 68

A second so-called "seminested" PCR was carried out with a 5' primer situated inside the region already amplified. This second PCR was carried out under the same experimental conditions as those used for the first PCR, using 10 µl of the amplification product derived from the first PCR.

Primers used for the seminested PCR:

- 5' primer, identified by SEQ ID NO: 70

5' CCA ATA GCC AGA CCA TTA TAT ACA CTA ATT 3';

- 3' primer, identified by SEQ ID NO: 68

The primers SEQ ID NO: 69 and SEQ ID NO: 70 are specific for the pol region of MRSV-1.

An amplification product of 1.9 Kb was obtained for the plasma of the MS patient. The corresponding fragment was not observed for the healthy control plasma. This amplification product was cloned in the following manner:

The amplified DNA was inserted into a plasmid with the aid of the TA Cloning kit®. The 2 µl of DNA solution were mixed with 5 µl of sterile distilled water, 1 µl of a 10 times concentrated ligation buffer "10X LIGATION BUFFER", 2 µl of "pCR™ VECTOR" (25 ng/ml) and 1 µl of "T4 DNA LIGASE". This mixture was incubated overnight at 12°C. The next steps were carried out in accordance with the instructions for the TA Cloning kit® (Invitrogen). At the end of the procedure, the white colonies of recombinant bacteria (white) were subcultured so as to be cultured and allow the

extraction of the plasmids incorporated according to the so-called "miniprep" procedure. The plasmid preparation of each recombinant colony was cut with an appropriate restriction enzyme and analyzed on agarose gel. The plasmids possessing an insert detected under UV light after staining the gel with ethidium bromide were selected for the sequencing of the insert after hybridization with a primer complementary to the Sp6 promoter present on the cloning plasmid of the TA cloning kit®. The reaction prior to the sequencing was then carried out according to the method recommended for using the sequencing kit "PRISM™ Ready Reaction AmpliTaq® FS, DyeDeoxy™ Terminator" (Applied Biosystems, ref. 402119) and the automated sequencing was carried out on the Applied Biosystems 373 A and 377 apparatus, according to the manufacturer's instructions.

The clone obtained contains a CL6-5' region encoding the N-terminal end of integrase and a CL6-3' region corresponding to the 3' terminal region of MSRV-1 and making it possible to define the end of the envelope (234 bp) and the U3 and R (401 bp) regions of the MSRV1 retrovirus.

The region corresponding to the N-terminal end of integrase is represented by its nucleotide sequence (SEQ ID NO: 112) in Figure 27. The three potential reading frames are presented by their amineo [sic] acid sequence under the nucleotide sequence, and the amineo [sic] acid sequence of the N-terminal end of integrase is identified by SEQID NO: 113.

The C16-3' region is represented by its nucleotide sequence (SEQ ID NO: 114) in Figure 3. The three potential reading frames are presented by their amineo [sic] acid sequence under the nucleotide sequence. An amineo [sic] acid sequence corresponding to the C-terminal end of the MSRV-1 env protein is identified by SEQ ID NO: 115.

In order to evaluate the promoter activity of the LTR obtained from clone 6 (c16), a test of promoter

activity using the enzyme CAT (chloramphenicol acetyl transferase) was carried out with the corresponding U3R region. In parallel, a clone containing the same U3R region of endogenous retroviral RNA expressed in normal placenta (PH74) and a clone (5M6) obtained from DNA were tested. The result presented in Figure 12 shows a very high promoter activity of the LTR derived from MS plasma (cl6) and a significantly much lower activity with the sequences of non-MS endogenous origin.

EXAMPLE 2: PREPARATION OF THE C15 CLONE CONTAINING THE REGION ENCODING A PORTION OF THE MSRV-1 RETROVIRUS ENVELOPE

A RT-PCR was carried out on the total RNA extracted from virions concentrated by ultra-centrifugation of a synoviocyte culture supernatant obtained from an MS patient. The synthesis of cDNA was carried out with an oligo dT primer and the reverse transcriptase "Expand™ RT" from Boehringer according to the conditions recommended by the company. A PCR was carried out with the Expand™ Long Template PCR System (Boehringer) under the following conditions: 94°C 5 min then 93°C 1 min, 60°C 1 min, 68°C 3 min over 40 cycles and 68°C for 8 min and with a final reaction volume of 50 µl.

Primers used for the PCR:

- 5' primer, identified by SEQ ID NO: 69

5' GCC ATC AAG CCA CCC AAG AAC TCT TAA CTT 3';

- 3' primer, identified by SEQ ID NO: 116

5' TGG GGT TCC ATT TGT AAG ACC ATC TGT AGC TT 3'

A second so-called "seminested" PCR was carried out with a 5' primer situated inside the region already amplified. This second PCR was carried out under the same experimental conditions as those used for the first PCR (except that 30 cycles were used instead of 40), using 10 µl of the amplification product derived from the first PCR.

Primers used for the seminested PCR:

- 5' primer, identified by SEQ ID NO: 70

5' CCA ATA GCC AGA CCA TTA TAT ACA CTA ATT 3';

- 3' primer, identified by SEQ ID NO: 116

The primers SEQ ID NO: 69 and SEQ ID NO: 70 are specific for the pol region of MRSV-1. The primer SEQ ID NO: 116 is specific for the sequence FBd13 (also called B13) and is located in the conserved env region among the oncoretroviruses.

An amplfication product of 1932 bp was obtained and cloned in the following manner:

the amplified DNA was inserted into a plasmid with the aid of the TA Cloning kit®. The various steps were carried out in accordance with the instructions for the TA Cloning kit® (Invitrogen). At the end of the procedure, the white colonies of recombinant bacteria (white) were subcultured so as to be cultured and allow the extraction of the plasmids incorporated according to the so-called "miniprep" procedure. The plasmid preparation of each recombinant colony was cut with an appropriate restriction enzyme and analyzed on agarose gel. The plasmids possessing an insert detected under UV light after staining the gel with ethidium bromide were selected for the sequencing of the insert after hybridization with a primer complementary to the SP6 promoter present on the cloning plasmid of the TA cloning kit®. The reaction prior to the sequencing was then carried out according to the method recommended for using the sequencing kit "PRISM™ Ready Reaction AmpliTaq® FS, DyeDeoxy™ Terminator" (Applied Biosystems, ref. 402119) and the automated sequencing was carried out on the Applied Biosystems 373 A and 377 apparatus, according to the manufacturer's instructions.

The C15 clone obtained contains a region corresponding to the region of the MSRV-1 envelope of 1481 bp.

The env region of the C15 clone is represented by its nucleotide sequence (SEQ ID NO: 117) in Figure 5. The three potential reading frames of this clone are presented by their amineo [sic] acid sequence

under the nucleotide sequence. The reading frame corresponding to an MSRV-1 structural env protein is identified by SEQ ID NO: 118.

From the defined sequences obtained from clones c16 and C15, it was possible to produce a plasmid construct encoding a complete envelope followed by the 3' LTR, as presented in Figure 13 with the corresponding reading frame.

EXAMPLE 3: PREPARATION OF A 5M6 CLONE CONTAINING THE SEQUENCES OF THE 3' TERMINAL REGION OF THE ENVELOPE, FOLLOWED BY THE MSRV-1 PROVIRAL TYPE U3, R AND U5 SEQUENCES

A monodirectional PCR was carried out on the DNA extracted from immortalized B lymphocytes in culture from an MS patient. The PCR was carried out with Expand™ Long Template PCR System (Boehringer) under the following conditions: 94°C 3 min then 93°C 1 min, 60°C 1 min, 68°C 3 min over 10 cycles, then 93°C 1 min, 60°C 1 min with 15 sec of extension at each cycle, 68°C 3 min over 35 cycles and 68°C for 7 min and with a final reaction volume of 50 µl.

The primer used for the PCR identified by SEQ ID NO: 119 is 5' TCA AAA TCG AAG AGC TTT AGA CTT GCT AAC CG 3';

The primers [sic] SEQ ID NO: 119 is specific for the env region of the C15 clone.

An amplification product of 1673 bp was obtained and cloned in the following manner:

the amplified DNA was inserted into a plasmid with the aid of the TA Cloning kit®. The various steps were carried out in accordance with the instructions for the TA Cloning kit® (Invitrogen). At the end of the procedure, the white colonies of recombinant bacteria (white) were subcultured so as to be cultured and allow the extraction of the plasmids incorporated according to the so-called "miniprep" procedure. The plasmid preparation of each recombinant colony was cut with an appropriate restriction enzyme and analyzed on agarose

gel. The plasmids possessing an insert detected under UV light after staining the gel with ethidium bromide were selected for the sequencing of the insert after hybridization with a primer complementary to the T7 promoter present on the cloning plasmid of the TA cloning kit®. The reaction prior to the sequencing was then carried out according to the method recommended for using the sequencing kit "PRISM™ Ready Reaction AmpliTaq® FS, DyeDeoxy™ Terminator" (Applied Biosystems, ref. 402119) and the automated sequencing was carried out on the Applied Biosystems 373 A and 377 apparatus, according to the manufacturer's instructions.

The 5M6 clone obtained contains a region corresponding to the 3' region of the MSRV-1 envelope of 492 bp followed by the regions U3, R and U5 (837 bp) of MSRV1.

The 5M6 clone is represented by its nucleotide sequence (SEQ ID NO: 120) in Figure 5. The three potential reading frames of this clone are presented by their amineo [sic] acid sequence under the nucleotide sequence. The reading frame corresponding to the C-terminal end of the MSRV-1 env protein is identified by SEQ ID NO: 121.

EXAMPLE 4: PREPARATION OF THE LB16 CLONE CONTAINING THE REGION ENCODING THE MSRV-1 RETROVIRUS INTEGRASE

An RT-PCR was carried out on the total RNA treated with DNAseI and extracted from a choroid plexus obtained from an MS patient. The synthesis of cDNA was carried out with an oligo dT primer and the reverse transcriptase "Expand™ RT" from Boehringer according to the conditions recommended by the company. A "no RT" control was carried out in parallel on the same material. A PCR was carried out with Taq polymerase (Perkin Elmer) under the following conditions: 95°C 5 min, then 95°C 1 min, 55°C 1 min, 72°C 2 min over 35 cycles and 72°C for 8 min and with a final reaction volume of 50 µl.

Primers used for the PCR:

- 5′ primer, identified by SEQ ID NO: 122

5′ GGC ATT GAT AGC ACC CAT CAG 3′;

- 3′ primer, identified by SEQ ID NO: 123

5′ CAT GTC ACC AGG GTG GAA TAG 3′

The primer SEQ ID NO: 122 is specific for the pol region of MSRV-1 and more precisely similar to the integrase region described above. The primer SEQ ID NO 123 was defined on sequences of the clones obtained during preliminary tests.

An amplification product of about 760 bp was obtained only in the test with RT and was cloned in the following manner:

the amplified DNA was inserted into a plasmid with the aid of the TA Cloning kit®. The various steps were carried out in accordance with the instructions for the TA Cloning kit® (Invitrogen). At the end of the procedure, the white colonies of recombinant bacteria (white) were subcultured so as to be cultured and allow the extraction of the plasmids incorporated according to the so-called "miniprep" procedure. The plasmid preparation of each recombinant colony was cut with an appropriate restriction enzyme and analyzed on agarose gel. The plasmids possessing an insert detected under UV light after staining the gel with ethidium bromide were selected for the sequencing of the insert after hybridization with a primer complementary to the T7 promoter present on the cloning plasmid of the TA cloning kit®. The reaction prior to the sequencing was then carried out according to the method recommended for using the sequencing kit "PRISM™ Ready Reaction AmpliTaq® FS, DyeDeoxy™ Terminator" (Applied Biosystems, ref. 402119) and the automated sequencing was carried out on the Applied Biosystems 373 A and 377 apparatus, according to the manufacturer's instructions.

The LB16 clone obtained contains the sequences corresponding to integrase. The nucleotide sequence of

this clone was identified by SEQ ID NO: 124 in Figure 11, three reading frames are determined.

EXAMPLE 5: PREPARATION OF A CLONE 2, CL2, CONTAINING IN 3' A PORTION HOMOLOGOUS TO THE POL GENE, CORRESPONDING TO THE PROTEASE GENE, AND TO THE GAG GENE (GM3) CORRESPONDING TO THE NUCLEOCAPSID, AND A NEW 5'CODING REGION, CORRESPONDING TO THE GAG GENE MORE SPECIFICALLY THE TEMPLATE AND THE CAPSID of MSRV-1.

A PCR amplification was carried out on the total RNA extracted from 100 µl of plasma from a patient suffering from MS. A water control, treated under the same conditions, was used as negative control. The synthesis of cDNA was carried out with 300 pmol of a random primer (GIBCO-BRL, France) and the reverse transcriptase "Expand RT" (BOEHRINGER MANNHEIM, France) according to the conditions recommended by the company. An amplification by PCR ("polymerase chain reaction") was carried out with the enzyme *Taq* polymerase (Perkin Elmer, France) using 10 µl of cDNA under the following conditions: 94°C 2 min, 55°C 1 min, 72°C 2 min then 94°C 1 min, 55°C 1 min, 72°C 2 min over 30 cycles and 72°C for 7 min with a final reaction volume of 50 µl.

Primers used for the PCR amplification:

- 5' primer, identified by SEQ ID NO: 126

5' CGG ACA TCC AAA GTG ATG GGA AAC G 3';

- 3' primer, identified by SEQ ID NO: 127

5' GGA CAG GAA AGT AAG ACT GAG AAG GC 3'

A second amplification by so-called "seminested" PCR was carried out with a 5' primer situated inside the region already amplified. This second PCR was carried out under the same experimental conditions as those used during the first PCR, using 10 µl of the amplification product derived from the first PCR.

Primers used for the amplification by seminested PCR:

- 5' primer, identified by SEQ ID NO: 128

5' CCT AGA ACG TAT TCT GGA GAA TTG GG 3';

- 3' primer, identified by SEQ ID NO: 129

5' TGG CTC TCA ATG GTC AAA CAT ACC CG 3'

The primers SEQ ID NO: [lacuna] and SEQ ID NO: [lacuna] are specific for the pol region, clone G+E+A, more specifically the E region: nucleotide position No. 423 to No. 448. The primers used in the 5' region were defined on sequences of clones obtained during preliminary tests.

An amplification product of 1511 bp was obtained from the RNA extracted from the plasma of an MS patient. The corresponding fragment was not observed for the water control. This amplification product was cloned in the following manner.

The amplified DNA was inserted into a plasmid with the aid of the TA Cloning kit™. The 2 µl of DNA solution were mixed with 5 µl of sterile distilled water, 1 µl of a 10 times concentrated ligation buffer "10X LIGATION BUFFER", 2 µl of "pCR™ VECTOR" (25 ng/ml)and 1 µl of "T4 DNA LIGASE". This mixture was incubated overnight at 14°C. The following steps were carried out in accordance with the instructions of the TA Cloning kit® (Invitrogen). The mixture was plated after transformation of the ligation into *E. coli* INVαF' bacteria. At the end of the procedure, the white colonies of recombinant bacteria were subcultured so as to be cultured and allow the extraction of the plasmids incorporated according to the so-called "DNA minipreparation" procedure (17). The plasmid preparation of each recombinant colony was cut with the restriction enzyme EcoRI and analyzed on agarose gel. The plasmids possessing an insert detected under UV light after staining the gel with ethidium bromide were selected for the sequencing of the insert after hybridization with a primer complementary to the T7 promoter present on the cloning plasmid of the TA cloning kit®. The reaction prior to the sequencing was then carried out according to the method recommended for using the sequencing kit "PRISM™ Ready Reaction Amplitaq® FS, DyeDeoxy™ Terminator" (Applied

Biosystems, ref. 402119) and the automated sequencing was carried out on the Applied Biosystems 373 A and 377 apparatus, according to the manufacturer's instructions.

The clone obtained, called CL2, contains a C-terminal region similar to the 5' terminal region of the clones G+E+A of MSRV-1, which makes it possible to define the C-terminal region of the gag gene and a new region corresponding to the N-terminal region of the MSRV-1 gag gene.

CL2 makes it possible to define a region of 1511 bp having an open reading frame in the N-terminal region of 1077 bp encoding 359 amino acids and a non-open reading frame of 454 bp corresponding to the C-terminal region of the MSRV-1 gag gene.

The nucleotide sequence of CL2 is identified by SEQ ID NO: 130. It is represented in Figure 6 with the potential reading frames in amineo [sic] acid.

The 1077 bp fragment of CL2 encoding 359 amino acids was amplified by PCR with the *Pwo* enzyme (5U/µl) (Boehringer Mannheim, France) using 1 µl of the DNA minipreparation of clone 2 under the following conditions: 95°C 1 min, 60°C 1 min, 72°C 2 min over 25 cycles and with a final reaction volume of 50 µl with the aid of the primers:

- 5' primer (*Bam*HI), identified by SEQ ID NO: 132
5' TGC TGG AAT TCG GGA TCC TAG AAC GTA TTC 3' (30 mer), and
- 3' primer (*Hind*III), identified by SEQ ID NO: 133
5 AGT TCT GCT CCG AAG CTT AGG CAG ACT TTT 3' (30 mer)

corresponding, respectively, to the nucleotide sequence of clone 2 at position -9 to 21 and 1066 to 1095.

The fragment obtained by PCR was linearized with *Bam*HI and *Hind*III and subcloned into the expression vectors pET28C and pET21C (NOVAGEN) linearized with *Bam*HI and *Hind*III. The sequencing of the DNA of the 1077 bp fragment of clone 2 in the two expression vectors was carried out according to the method recommended for the use of the sequencing kit

"PRISM™ Ready Reaction Amplitaq® FS, DyeDeoxy™ Terminator" (Applied Biosystems, ref. 402119) and the automated sequencing was carried out on the Applied Biosystems 373 A and 377 apparatus, according to the manufacturer's instructions.

The expression of the nucleotide sequence of the 1077 bp fragment of clone 2 by the expression vectors pET28C and pET21C are identified by SEQ ID NO: 135 and SEQ ID NO: 137, respectively.

EXAMPLE 6: EXPRESSION OF CLONE 2 IN *ESCHERICHIA COLI*

The constructs pET28c-clone 2 (1077 bp) and pET21C-clone 2 (1077 bp) synthesize, in the bacterial strain BL21 (DE3), a protein fused at the N- and C-terminus for the vector pET28C and the C-terminus for the vector pET21C with 6 Histidines, having an apparent molecular mass of about 45 kDa, identified by SDS-PAGE polyacrylamide gel electrophoresis (SDS = Sodium Dodecyl Sulfate) (Laemmli, 1970 (1)). The reactivity of the protein was demonstrated towards an anti-Histidine monoclonal antibody (DIANOVA) by the Western-blot technique (Towbin et al., 1979 (2)).

The recombinant proteins pET28c-clone 2 (1077 bp) and pET21C-clone 2 (1077 bp) were visualized by SDS-PAGE in the insoluble fraction after enzymatic digestion of the bacterial extracts with 50 µl of lysozyme (10 mg/ml) and ultrasound lysis.

The antigenic properties of the recombinant antigens pET28C-clone 2 (1077 bp) and pET21C-clone 2 (1077 bp) were tested by Westen blotting () [sic] after solubilization of the bacterial pellet with 2% SDS and 50 mM β-mercaptoethanol. After incubation with sera from patients suffering from multiple sclerosis, the sera from neurological controls and the sera from controls at the Blood Transfusion Center (CTS), the immunocomplexes were detected with the aid of an alkaline phosphatase-coupled goat serum anti-human IgG and anti-human IgM.

The results are presented in the table below.

TABLE

Reactivity of sera affected by multiple sclerosis and controls with the MSRV-1 recombinant protein gag clone 2 (1077 bp) = pET21C-clone 2 (1077 bp) and pET28C-clone 2 (1077 bp)[a]

DISEASE	NUMBER OF INDIVIDUALS TESTED	NUMBER OF POSITIVE INDIVIDUALS
MS	15	6 2(+++), 2(++), (2(+)
NEUROLOGICAL CONTROLS	2	1(+++)
HEALTHY CONTROLS (CTS)	22	1(+/-)

(a) The strips containing 1.5 µg of recombinant antigen pET-gag clone 2 (1077 bp) exhibit reactivity against sera diluted 1/100. The Western-Blot interpretation is based on the presence or absence of a specific pET-gag clone 2 (1077 bp) band on the strips. Positive and negative controls are included in each experiment.

These results show that, under the technical conditions used, about 40% of the human sera affected by multiple sclerosis which were tested react with the recombinant proteins pET28C-clone 2 (1077 bp) and pET21C-clone 2 (1077 bp). Reactivity was observed on a neurological control and it is of interest to note that the RNAs extracted from this serum, after the reverse transcriptase step, are also amplified by PCR in the pol region. This suggests that people who have not declared MS may also harbor and express this virus. On the other hand, an apparently healthy control (CTS donor) possesses anti-gag (clone 2, 1077 bp) antibodies. This is compatible with an immunity acquired against MSRV-1 independently of a declared associated autoimmune disease.

EXAMPLE 7: PREPARATION OF AN LB13 CLONE CONTAINING IN 3' A PORTION HOMOLOGOUS TO CLONE 2 CORRESPONDING TO THE GAG GENE AND IN 5' A PORTION HOMOLOGOUS TO THE 5M6 CLONE CORRESPONDING TO THE U5 LTR REGION

An RT-PCR ("reverse transcriptase-polymerase chain reaction") was carried out using total RNA extracted from virions, obtained from supernatants of B lymphocyte cells of patients suffering from multiple sclerosis, concentrated by ultracentrifugations. The synthesis of cDNA was carried out with a specific primer SEQ No. XXX and the reverse transcriptase "Expand™ RT" from BOEHRINGER MANNHEIM according to the conditions recommended by the company.

Primer used for the synthesis of the cDNA, identified by SEQ ID NO: 138:

5' CTT GGA GGG TGC ATA ACC AGG GAA T 3'

A PCR amplification was carried out with *Taq* polymerase (Perkin Elmer, France) under the following conditions: 94°C 1 min, 55°C 1 min, 72°C 2 min over 35 cycles at 72°C for 7 min and with a final reaction volume of 100 µl.

Primers used for the PCR amplification:

- 5' primer, identified by SEQ ID NO: 139

5' TGT CCG CTG TGC TCC TGA TC 3'

- 3' primer, identified by SEQ ID NO: 138

5' CTT GGA GGG TGC ATA ACC AGG GAA T 3'

A second so-called "seminested" PCR amplification was carried out with a 3' primer situated inside the region already amplified. This second amplification was carried out under the same experimental conditions as those used during the first amplification, using 10 µl of the amplification product derived from the first PCR.

Primers used for the "seminested" PCR amplification:

- 5' primer, identified by SEQ ID NO: 139

5' TGT CCG CTG TGC TCC TGA TC 3'

- 3' primer, identified by SEQ ID NO: 140

5' CTA TGT CCT TTT GGA CTG TTT GGG T 3'

The primers SEQ ID NO: 138 and SEQ ID NO: 140 are specific for the gag region, clone 2 nucleotide position No. 373-397 and No. 433-456. The primers used in the 5' region were defined on sequences of the clones obtained during preliminary tests.

An amplification product of 764 bp was obtained and cloned in the following manner:

The amplified DNA was inserted into a plasmid with the aid of the TA Cloning kit™. The 2 µl of DNA solution were mixed with 5 µl of sterile distilled water, 1 µl of a 10 times concentrated ligation buffer "10X LIGATION BUFFER", 2 µl of "pCR™ VECTOR" (25 ng/ml)and 1 µl of "T4 DNA LIGASE". This mixture was incubated overnight at 14°C. The following steps were carried out in accordance with the instructions of the TA Cloning kit® (Invitrogen). The mixture was plated after transformation of the ligation into *E. coli* INVαF' bacteria. At the end of the procedure, the white colonies of recombinant bacteria were subcultured so as to be cultured and allow the extraction of the plasmids incorporated according to the so-called "DNA minipreparation" procedure (17). The plasmid preparation of each recombinant colony was cut with the restriction enzyme *Eco*RI and analyzed on agarose gel. The plasmids possessing an insert detected under UV light after staining the gel with ethidium bromide were selected for the sequencing of the insert after hybridization with a primer complementary to the T7 promoter present on the cloning plasmid of the TA cloning kit®. The reaction prior to the sequencing was then carried out according to the method recommended for using the sequencing kit "PRISM™ Ready Reaction Amplitaq® FS, DyeDeoxy™ Terminator" (Applied Biosystems, ref. 402119) and the automated sequencing was carried out on the Applied Biosystems 373 A and 377 apparatus, according to the manufacturer's instructions.

The LB13 clone obtained contains an N-terminal region of MSRV-1 gag gene homologous to clone 2 and an

LTR corresponding to a portion of the U5 region. Between the U5 region and gag, a binding site for the transfer RNAs, the PBS "primer binding site", was identified.

The nucleotide sequence of the 764 bp fragment of the LB13 clone in the plasmid "pCR™ vector" is represented in the identifier SEQ ID NO: 141.

The binding site for the transfer RNAs, having a sequence of PBS tryptophan type, was identified at nucleotide position No. 342-359 of the LB13 clone.

As this same PBS was found in the endogenous copies homologous to MSRV1, the endogenous family thus defined is henceforth called HERV W, according to the nomenclature proposed for the endogenous retrovirus families (W=tryptophan).

A short ORF of about 65 amino acids was found in the U5 region of the 5' LTR of the LB13 clone.

Sequence of the ORF:

PMASNRAITLTAWSKIPFLGIRETKNPRSENTRLATMLEAAHHHFGSSPPLSWEL WEQGPQVTIW.

The corresponding nucleotide sequence starting at an ATG codon is capable of being expressed in a subgenomic DNA from a proviral LTR (U3RU5).

Another clone, called LA15, was obtained on the total RNA extracted from virions concentrated by ultracentrifugation from a culture supernatant of synoviocytes obtained from a patient suffering from rheumatoid arthritis. The strategy for amplifying and cloning the LA15 clone is exactly the same which was used for the LB13 clone.

The nucleotide sequence of the LA15 clone, which is represented in the identifier SEQ ID NO: 142, is very similar to the LD13 clone. This suggests that the MSVR-1 retrovirus detected in multiple sclerosis has sequences which are similar to those found in rheumatoid arthritis.

EXAMPLE 8: RECONSTRUCTION OF AN RU5-GAG REGION FROM THE CLONES LB15, LB13, CL2 AND CL17

The clones CL2 and LB13 have already been described in the preceding examples. The LB15 clone was obtained using the R sequence of the LTR of the cl6 clone in order to define a primer in 5' and the anti-sense primers used are the same as for the LB13 clone. The CL17 clone was obtained by nested RT-PCR using the following primers:

5'-TCATGCAACTGCACTCTTCTGGTCCG-3' (sense)
5'-TCTTGCACTAACCTCCACTGTCCGTTGG-3' (antisense)

5'-ATCCCCCAGTAACAATTTGGTGACCACG-3' (sense)
5'-TCGGGTCTAAGAGGGTACTTCCTTTGGTAGG-3' (antisense)

The LB15 clone was obtained from virions obtained by culturing MS cells. The LB17 clone was obtained from culturing plasma from an MS patient.

These overlapping clones made it possible to reconstruct an RU5-gag sequence with a potential ORF in the gag gene, as presented in Figure 14.

EXAMPLE 9: PREPARATION OF A CLONE 87-23

The region corresponding to integrase was amplified and cloned from MS plasma using a seminested RT PCR with the following primers situated in the pol and env regions of MSRV1.

In the pol region:

5'-TTACGCAGGTCTCAGGGATGAGCTT-3' (sense-primary PCR)
5'-CGGCAGTAGCAGTCTTAGTATCTGAAGCAGTTA-3' (sense-secondary PCR)

In the env region,

5'-GGTACGGAGGGTTTCATGTAGTTTTGAG-3' (anti-sense primary and secondary PCR)

The amplified clone contains 774 bp in the pol/RT region, all the integrase region (1197 bp) and

the start of the env region (480 bp). The nucleotide sequence corresponding to the integrase region and the translation to amino acids of the potential ORF are presented in Figure 15.

EXAMPLE 10: CONFIRMATION OF THE PRESENCE OF RNA CONTAINING ENV SEQUENCES RELATED TO ERV9 IN THE RETROVIRAL PARTICLES ASSOCIATED WITH THE MSRV1 GENOME:

Sequences related to ERV9 have been found in a minor proportion in the virion preparations obtained from MS compared with the MSRV1 sequences. The existence of phenomena of co-encapsidation of phylogenetically related endogenous sequences into retroviral particles produced by a replicative strain has been described. Surprisingly, an RNA region comprising an ORF starting in the 3' portion of env and continuing potentially into the 3' LTR has been found in various MS samples. In order to specify the existence of an ORF, transcription-translation tests were carried out and made it possible to show the reality of an env ORF containing the entire transmembrane (TM) portion and ending at the start of the putative LTR. However, an additional frame (ORFX) follows and continues in the 3' LTR. The two products of expression were visualized and their respective ORFs were subcloned. Figure 16 represents the nucleotide and peptide sequences of the B13 clone already described, specifying the ORFs in the truncated env region and in the putative LTR. The presence of such RNAs may be responsible for recombinations with the replicative strain and consequently generate strains having a modified pathogenicity.

BIBLIOGRAPHIC REFERENCES

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(2) Towbin H., Staehelin T. & Gordon J. Electrophoretic transfer of proteins from polyacryalmide gels to nitrocellulose sheets: procedure and some applications. Proc. Natl. Acad. Sci. USA. (1979). **76**: 4350-4354.

CLAIMS

1. Nucleic material, in isolated or purified state, comprising a nucleotide sequence chosen from the group which consists of (i) the sequences SEQ ID NO: 112, SEQ ID NO: 114, SEQ ID NO: 117, SEQ ID NO: 120, SEQ ID NO: 124, SEQ ID NO: 130, SEQ ID NO: 141 and SEQ ID NO: 142; (ii) the sequences complementary to sequences (i); and (iii) the sequences equivalent to sequences (i) or (ii), in particular the sequences having, for every series of 100 contiguous monomers, at least 50%, and preferentially at least 70% homology with sequences (i) or (ii) respectively.

2. Nucleic material, in isolated or purified state, encoding a polypeptide having, for every contiguous series of at least 30 amino acids, at least 50%, and preferably at least 70% homology with a peptide sequence chosen from the group which consists of SEQ ID NO: 113, SEQ ID NO: 115, SEQ ID NO: 118, SEQ ID NO: 121, SEQ ID NO: 135 and SEQ ID NO: 137.

3. Retroviral nucleic material, whose pol gene comprises a nucleotide sequence identical or equivalent to a sequence chosen from the group which consists of SEQ ID NO: 112, SEQ ID NO: 124 and their complementary sequences.

4. Retroviral nucleic material, in which the 5' end of the pol gene starts at nucleotide 1419 of SEQ ID NO: 130.

5. Retroviral nucleic material, in which the pol gene encodes a polypeptide having, for every contiguous series of at least 30 amino acids, at least 50%, and preferably at least 70% homology with the peptide sequence SEQ ID NO: 113.

6. Retroviral nucleic material, in which the 3' end of the gag gene ends at nucleotide 1418 of SEQ ID NO: 130.

7. Retroviral nucleic material, in which the env gene comprises a nucleotide sequence identical or

equivalent to a sequence chosen from the group which consists of SEQ ID NO: 117, and its complementary sequences.

8. Retroviral nucleic material, in which the env gene comprises a nucleotide sequence which starts at nucleotide 1 of SEQ ID NO: 117 and ends at nucleotide at nucleotide [sic] 233 of SEQ ID NO: 114.

9. Retroviral nucleic material, in which the env gene encodes a polypeptide having, for every contiguous series of at least 30 amino acids, at least 50%, and preferably at least 70% homology with the sequence SEQ ID NO: 118.

10. Retroviral nucleic material in which the U3R region of the 3' LTR comprises a nucleotide sequence which ends at nucleotide 617 of SEQ ID NO: 114.

11. Retroviral nucleic material in which the RU5 region of the 5' LTR comprises a nucleotide sequence which starts at nucleotide 755 of SEQ ID NO: 120 and ends at nucleotide 337 of SEQ ID NO: 141 or SEQ ID NO: 142.

12. Retroviral nucleic material comprising a sequence which starts at nucleotide 755 of SEQ ID NO: 120 and which ends at nucleotide 617 of SEQ ID NO: 114.

13. Retroviral nucleic material according to any one of the preceding claims, characterized in that it is associated with at least one autoimmune disease such as multiple sclerosis or rheumatoid arthritis.

14. Nucleotide fragment comprising a nucleotide sequence chosen from the group which consists of (i) the sequences SEQ ID NO: 112, SEQ ID NO: 114, SEQ ID NO: 117, SEQ ID NO: 120, SEQ ID NO: 124, SEQ ID NO: 130, SEQ ID NO: 141 and SEQ ID NO: 142; (ii) the sequences complementary to sequences (i); and (iii) the sequences equivalent to sequences (i) or (ii), in particular the sequences having, for every series of 100 contiguous monomers, at least 50%, and preferentially at least 70% homology with sequences (i) or (ii) respectively.

15. Nucleotide fragment according to Claim 14, consisting of a nucleotide sequence chosen from the group which consists of (i) the sequences SEQ ID NO: 112, SEQ ID NO: 114, SEQ ID NO: 117, SEQ ID NO: 120, SEQ ID NO: 124, SEQ ID NO: 130, SEQ ID NO: 141 and SEQ ID NO: 142; (ii) the sequences complementary to sequences (i); and (iii) the sequences equivalent to sequences (i) or (ii), in particular the sequences having, for every series of 100 contiguous monomers, at least 50%, and preferentially at least 70% homology with sequences (i) or (ii) respectively.

16. Nucleotide fragment comprising a nucleotide sequence encoding a polypeptide having, for every contiguous series of at least 30 amino acids, at least 50%, and preferably at least 70% homology with a peptide sequence chosen from the group which consists of SEQ ID NO: 113, SEQ ID NO: 115, SEQ ID NO: 118, SEQ ID NO: 121, SEQ ID NO: 135 and SEQ ID NO: 137.

17. Nucleotide fragment according to claim 16, consisting of a nucleotide sequence encoding a polypeptide having, for every contiguous series of at least 30 amino acids, at least 50%, and preferably at least 70% homology with a peptide sequence chosen from the group which consists of SEQ ID NO: 113, SEQ ID NO: 115, SEQ ID NO: 118, SEQ ID NO: 121, SEQ ID NO: 135 and SEQ ID NO: 137.

18. Nucleic probe for the detection of a retrovirus associated with multiple sclerosis and/or rheumatoid arthritis, characterized in that it is capable of hybridizing specifically with any fragment according to any one of claims 14 to 17, belonging to the genome of said retrovirus.

19. Probe according to claim 18, characterized in that it possesses from 10 to 100 nucleotides, preferably from 10 to 30 nucleotides.

20. Primer for the amplification, by polymerization, of an RNA or of a DNA of a retrovirus associated with multiple sclerosis and/or rheumatoid

arthritis, characterized in that it comprises a nucleotide sequence identical or equivalent to at least a portion of the nucleotide sequence of a fragment according to any one of claims 8 to 11, in particular a nucleotide sequence having, for every series of 10 contiguous monomers, at least 50%, preferably at least 70% homology with at least said portion of said fragment.

21. Primer according to claim 20, characterized in that its nucleotide sequence is chosen from SEQ ID NO: 116, SEQ ID NO: 119, SEQ ID NO: 122, SEQ ID NO: 123, SEQ ID NO: 126, SEQ ID NO: 127, SEQ ID NO: 128, SEQ ID NO: 129, SEQ ID NO: 132, and SEQ ID NO: 133.

22. RNA or DNA, and in particular replication and/or expression vector, comprising a genomic fragment of the nucleic material according to any one of claims 1 to 7 or a fragment according to any one of claims 14 to 17.

23. Peptide encoded by any open reading frame belonging to a nucleotide fragment according to any one of claims 14 to 17, in particular a polypeptide, for example oligopeptide forming or comprising an antigenic determinant recognized by sera of patients infected with the MSRV-1 virus, and/or in whom the MSRV-1 virus has been reactivated.

24. Peptide according to claim 23 comprising a sequence identical, partially or completely, or equivalent to a sequence chosen from SEQ ID NO: 113, SEQ ID NO: 115, SEQ ID NO: 118, SEQ ID NO: 121, SEQ ID NO: 135 and SEQ ID NO: 137.

25. Diagnostic, prophylactic or therapeutic composition, in particular for inhibiting the expression of at least one retrovirus associated with multiple sclerosis and/or rheumatoid arthritis, comprising a nucleotide fragment according to any one of claims 14 to 17.

26. Method for detecting a retrovirus associated with multiple sclerosis and/or rheumatoid arthritis, in a biological sample, characterized in that an RNA and/or a DNA assumed to belong to or obtained from said retrovirus, or their complementary RNA and/or DNA, is brought into contact with a composition comprising a nucleotide fragment according to any one of claims 14 to 17.

FIG 1

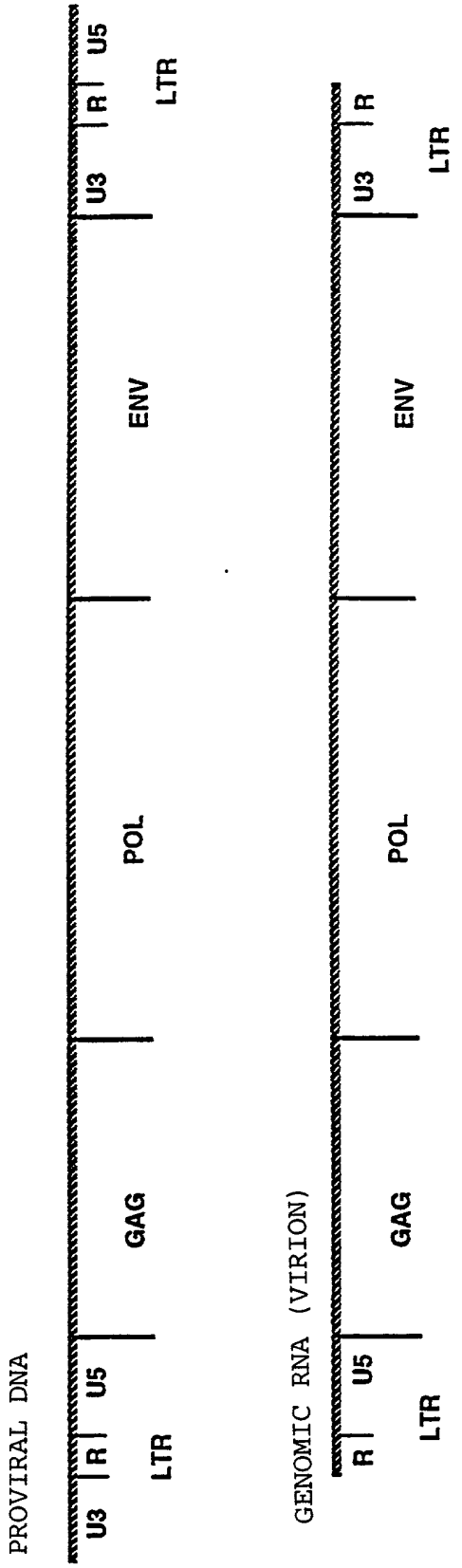

PROVIRAL DNA
U3
R
U5
LTR
GAG
POL
ENV
U3
R
U5
LTR
GENOMIC RNA (VIRION)
R
U5
LTR
GAG
POL
ENV
U3
R
LTR

FIG 2

```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
GCTTATAGAA GGACCCCTAG TATGGGGTAA TCCCCTCTGG GAAACCAAGC      50
A Y R R T P S M G . S P L G N Q A
 L I E G P L V W G N P L W E T K P
  L . K D P . Y G V I P S G K P S

CCCAGTACTC AGCAGGAAAA ATAGAATAGG AAACCTCACA AGGACATACT     100
 P V L S R K N R I G N L T R T Y F
  Q Y S A G K I E . E T S Q G H T
P S T Q Q E K . N R K P H K D I L

TTCCTCCCCT CCAGATGGCT AGCCACTGAG GAAGGAAAAA TACTTTCACC     150
  P P L Q M A S H . G R K N T F T
F L P S R W L A T E E G K I L S P
 S S P P D G . P L R K E K Y F H L

TGCAGCTAAC CAACAGAAAT TACTTAAAAC CCTTCACCAA ACCTTCCACT     200
C S . P T E I T . N P S P N L P L
 A A N Q Q K L L K T L H Q T F H L
  Q L T N R N Y L K P F T K P S T

TAGGCATTGA TAGCACCCAT CAGATGGCCA AATTATTATT TACTGGACCA     250
 R H . . H P S D G Q I I I Y W T R
  G I D S T H Q M A K L L F T G P
. A L I A P I R W P N Y Y L L D Q

GGCCTTTTCA AAACTATCAA GAAGATAGTC AGGGGCTGTG AAGTGTGCCA     300
  P F Q N Y Q E D S Q G L . S V P
G L F K T I K K I V R G C E V C Q
 A F S K L S R R . S G A V K C A K

AAGAAATAAT                                                 310
K K .
 R N N
  E I
```

FIG 2 (continued)

```
      10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
CCCTGTATCT TTAACCTCCT TGTTAAGTTT GTCTCTTCCA GAATCAAAAC   50
P  C  I  F  N  L  L  V  K  F  V  S  S  R  I  K  T
 P  V  S  L  T  S  L  L  S  L  S  L  P  E  S  K  L
  L  Y  L  .  P  P  C  .  V  C  L  F  Q  N  Q  N

TGTAAAACTA CAAATTGTTC TTCAAATGGA GCACCAGATG GAGTCCATGA  100
 V  K  L  Q  I  V  L  Q  M  E  H  Q  M  E  S  M  T
  .  N  Y  K  L  F  F  K  W  S  T  R  W  S  P  .
C  K  T  T  N  C  S  S  N  G  A  P  D  G  V  H  D

CTAAGATCCA CCGTGGACCC CTGGACCGGC CTGCTAGCCC ATGCTCCGAT  150
  K  I  H  R  G  P  L  D  R  P  A  S  P  C  S  D
L  R  S  T  V  D  P  W  T  G  L  L  A  H  A  P  M
 .  D  P  P  W  T  P  G  P  A  C  .  P  M  L  R  C

GTTAATGACA TTGAAGGCAC CCCTCCCGAG GAAATCTCAA CTGCACAACC  200
V  N  D  I  E  G  T  P  P  E  E  I  S  T  A  Q  P
 L  M  T  L  K  A  P  L  P  R  K  S  Q  L  H  N  P
  .  .  H  .  R  H  P  S  R  G  N  L  N  C  T  T

CCTACTATGC CCCAATTCAG CGGGAAGCAG TTAGAGCGGT CATCAGCCAA  250
 L  L  C  P  N  S  A  G  S  S  .  S  G  H  Q  P  T
  Y  Y  A  P  I  Q  R  E  A  V  R  A  V  I  S  Q
P  T  M  P  Q  F  S  G  K  Q  L  E  R  S  S  A  N

CCTCCCCCAAC AGCACTTGGG TTTTCCTGTT GAGAGGGGGG ACTGAGAGAC  300
  S  P  T  A  L  G  F  S  C  .  E  G  G  L  R  D
P  P  Q  Q  H  L  G  F  P  V  E  R  G  D  .  E  T
 L  P  N  S  T  W  V  F  L  L  R  G  G  T  E  R  Q

AGGACTAGCT GGATTTCCTA GGCCAACGAA GAATCCCTAA GCCTAGCTGG  350
R  T  S  W  I  S  .  A  N  E  E  S  L  S  L  A  G
 G  L  A  G  F  P  R  P  T  K  N  P  .  A  .  L  G
  D  .  L  D  F  L  G  Q  R  R  I  P  K  P  S  W
```

FIG 3

```
         10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
GAAGGTGACT GCATCCACCT CTAAACATGG GGCTTGCAAC TTAGCTCACA   400
 K  V  T   A  S  T  S   K  H  G   A  C  N   L  A  H  T
  R  .  L   H  P  P   L  N  M  G   L  A  T   .  L  T
E  G  D  C   I  H  L   .  T  W  G   L  Q  L   S  S  H

CCCGACCAAT CAGAGAGCTC ACTAAAATGC TAATTAGGCA AAAATAGGAG   450
  R  P  I   R  E  L   T  K  M  L   I  R  Q   K  .  E
P  D  Q  S   E  S  S   L  K  C   .  L  G  K   N  R  R
 P  T  N   Q  R  A  H   .  N  A   N  .  A  K   I  G  G

GTAAAGAAAT AGCCAATCAT CTATTGCCTG AGAGCACAGC GGGAGGGACA   500
V  K  K   .  P  I  I   Y  C  L   R  A  Q  R   E  G  Q
 .  R  N   S  Q  S  S   I  A  .   E  H  S  G   R  D  K
  K  E  I   A  N  H  L   L  P  E   S  T  A  G   G  T

AGGATCGGGA TATAAACCCA GGCATTCGAG CCGGCAACGG CAACCCCCTT   550
 G  S  G   Y  K  P  R   H  S  S   R  Q  R   Q  P  P  L
  D  R  D   I  N  P  G   I  R  A   G  N  G   N  P  L
R  I  G  I   .  T  Q  A   F  E  P   A  T  A   T  P  F

TGGGTCCCCT CCCTTTGTAT GGGCGCTCTG TTTTCACTCT ATTTCACTCT   600
  G  P  L   P  L  Y  G   R  S  V   F  T  L   F  H  S
W  V  P  S   L  C  M  G   A  L  F   S  L  Y   F  T  L
 G  S  P   P  F  V  W   A  L  C   F  H  S   I  S  L  Y

ATTAAATCTT GCAACTGAAA AAAAAAAAAA AAAAA                   635
I  K  S  C   N  .  K  K   K  K  K
 L  N  L   A  T  E  K   K  K  K   K
  .  I  L   Q  L  K  K   K  K  K   K
```

FIG 4

```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
ATGGCCCTCC CTTATCATAC TTTTCTCTTT ACTGTTCTCT TACCCCCTTT      50
M A L P  Y H T  F L F  T V L L  P P F
 W P S  L I I L  F S L  L F S  Y P L S
  G P P  L S Y  F S L Y  C S L  T P F

CGCTCTCACT GCACCCCCTC CATGCTGCTG TACAACCAGT AGCTCCCCTT     100
 A L T  A P P P  C C C  T T S  S S P Y
  L S L  H P L  H A A V  Q P V  A P L
R S H C  T P S  M L L  Y N Q .  L P L

ACCAAGAGTT TCTATGAAGA ACGCGGCTTC CTGGAAATAT TGATGCCCCA     150
  Q E F  L . R  T R L P  G N I  D A P
T K S F  Y E E  R G F  L E I L  M P H
 P R V  S M K N  A A S  W K Y  . C P I

TCATATAGGA GTTTATCTAA GGGAAACTCC ACCTTCACTG CCCACACCCA     200
S Y R S  L S K  G N S  T F T A  H T H
 H I G  V Y L R  E T P  P S L  P T P I
  I . E  F I .  G K L H  L H C  P H P

TATGCCCCGC AACTGCTATA ACTCTGCCAC TCTTTGCATG CATGCAAATA     250
 M P R  N C Y N  S A T  L C M  H A N T
  C P A  T A I  T L P L  F A C  M Q I
Y A P Q  L L .  L C H  S L H A  C K Y

CTCATTATTG GACAGGGAAA ATGATTAATC CTAGTTGTCC TGGAGGACTT     300
  H Y W  T G K  M I N P  S C P  G G L
L I I G  Q G K  . L I  L V V L  E D L
 S L L  D R E N  D . S  . L S  W R T W

GGAGCCACTG TCTGTTGGAC TTACTTCACC CATACCAGTA TGTCTGATGG     350
G A T V  C W T  Y F T  H T S M  S D G
 E P L  S V G L  T S P  I P V  C L M G
  S H C  L L D  L L H P  Y Q Y  V . W
```

FIG 4 (continued)

```
      10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
ACCTCACCTG TGTAAAATTT AGCAATACTA TAGACACAAC CAGCTCCCAA   750
  L T C  V K F  S N T I  D T T  S S Q
T S P V  . N L  A I L  . T Q P  A P N
 P H L  C K I  .  Q Y Y  R H N  Q L P M

TGCATCAGGT GGGTAACACC TCCCACACGA ATAGTCTGCC TACCCTCAGG   800
C I R W  V T P  P T R  I V C L  P S G
 A S G  G . H L  P H E  . S A  Y P Q E
  H Q V  G N T  S H T N  S L P  T L R

AATATTTTTT GTCTGTGGTA CCTCAGCCTA TCATTGTTTG AATGGCTCTT   850
 I F F  V C G T  S A Y  H C L  N G S S
  Y F L  S V V  P Q P I  I V .  M A L
N I F C  L W Y  L S L  S L F E  W L F

CAGAATCTAT GTGCTTCCTC TCATTCTTAG TGCCCCCTAT GACCATCTAC   900
  E S M  C F L  S F L V  P P M  T I Y
Q N L C  A S S  H S .  C P L .  P S T
 R I Y  V L P L  I L S  A P Y  D H L H

ACTGAACAAG ATTTATACAA TCATGTCGTA CCTAAGCCCC ACAACAAAAG   950
T E Q D  L Y N  H V V  P K P H  N K R
 L N K  I Y T I  M S Y  L S P  T T K E
  . T R  F I Q  S C R T  . A P  Q Q K

AGTACCCATT CTTCCTTTTG TTATCAGAGC AGGAGTGCTA GGCAGACTAG  1000
 V P I  L P F V  I R A  G V L  G R L G
  Y P F  F L L  L S E Q  E C .  A D .
S T H S  S F C  Y Q S  R S A R  Q T R

GTACTGGCAT TGGCAGTATC ACAACCTCTA CTCAGTTCTA CTACAAACTA  1050
  T G I  G S I  T T S T  Q F Y  Y K L
V L A L  A V S  Q P L  L S S T  T N Y
 Y W H  W Q Y H  N L Y  S V L  L Q T I
```

FIG 4 (continued)

```
          10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
TCTCAAGAAA TAAATGGTGA CATGGAACAG GTCACTGACT CCCTGGTCAC  1100
S Q E I   N G D   M E Q   V T D S   L V T
 L K K  .  M V T   W N R   S L T   P W S P
  S R N   K W .   H G T G   H . L   P G H

CTTGCAAGAT CAACTTAACT CCCTAGCAGC AGTAGTCCTT CAAAATCGAA  1150
 L Q D   Q L N S   L A A   V V L   Q N R R
  C K I   N L T   P . Q Q   . S F   K I E
L A R S   T . L   P S S   S S P S   K S K

GAGCTTTAGA CTTGCTAACC GCCAAAAGAG GGGGAACCTG TTTATTTTTA  1200
  A L D   L L T   A K R G   G T C   L F L
E L . T   C . P   P K E   G.E P V   Y F .
 S F R   L A N R   Q K R   G N L   F I F R

GGAGAAGAAC GCTGTTATTA TGTTAATCAA TCCAGAATTG TCACTGAGAA  1250
G E E R   C Y Y   V N Q   S R I V   T E K
 E K N   A V I M   L I N   P E L   S L R K
  R R T   L L L   C . S I   Q N C   H . E

AGTTAAAGAA ATTCGAGATC GAATACAATG TAGAGCAGAG GAGCTTCAAA  1300
 V K E   I R D R   I Q C   R A E   E L Q N
  L K K   F E I   E Y N V   E Q R   S F K
S . R N   S R S   N T M  . S R G   A S K

ACACCGAACG CTGGGGCCTC CTCAGCCAAT GGATGCCCTG GGTTCTCCCC  1350
  T E R   W G L   L S Q W   M P W   V L P
T P N A   G A S   S A N   G C P G   F S P
 H R T   L G P P   Q P M   D A L   G S P L

TTCTTAGGAC CTCTAGCAGC TCTAATATTG TTACTCCTCT TTGGACCCTG  1400
F L G P   L A A   L I L   L L L F   G P C
 S . D   L . Q L  . Y C   Y S S   L D P V
  L R T   S S S   S N I V   T P L   W T L
```

FIG 4 (continued)

```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
TATCTTTAAC CTCCTTGTTA AGTTTGTCTC TTCCAGAATT GAAGCTGTAA   1450
 I  F  N   L  L  V  K   F  V  S   S  R  I   E  A  V  K
  S  L  T   S  L  L   S  L  S  L   P  E  L   K  L  .
Y  L  .  P   P  C  .   V  C  L   F  Q  N  .   S  C  K

AGCTACAGAT GGTCTTACAA ATGGAACCCC A                      1481
  L  Q  M   V  L  Q   M  E  P
S  Y  R  W   S  Y  K   W  N  P
 A  T  D   G  L  T  N   G  T  P
```

FIG 5

```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
TCAAAATCGA AGAGCTTTAG ACTTGCTAAC CGCCAAAAGA GGGGGAACCT   50
S K S K  S F R  L A N  R Q K R  G N L
 Q N R  R A L D  L L T  A K R  G G T C
  K I E  E L .  T C .  P P K E  G E P

GTTTATTTTT AGGGGAAGAA TGCTGTTAGT ATGTTAATCA ATCTGGAATC  100
 F I F  R G R M  L L V  C . S  I W N H
  L F L  G E E  C C .  Y V N Q  S G I
V Y F .  G K N  A V S  M L I N  L E S

ATTACTGAGA AAGTTAAAGA AATTTGAGAT CGAATATAAT GTAGAGCAGA  150
  Y . E  S . R  N L R S  N I M  . S R
I T E K  V K E  I . D  R I .  C R A E
 L L R  K L K K  F E I  E Y N  V E Q R

GGACCTTCAA AACACTGCAC CCTGGGGCCT CCTCAGCCAA TGGATGCCCT  200
G P S K  H C T  L G P  P Q P M  D A L
 D L Q  N T A P  W G L  L S Q  W M P W
  T F K  T L H  P G A S  S A N  G C P

GGACTCTCCC CTTCTTAGGA CCTCTAGCAG CTATAATATT TTTACTCCTC  250
 D S P  L L R T  S S S  Y N I  F T P L
  T L P  F L G  P L A A  I I F  L L L
G L S P  S . D  L . Q  L . Y F  Y S S

TTTGGACCCT GTATCTTCAA CTTCCTTGTT AAGTTTGTCT CTTCCAGAAT  300
  W T L  Y L Q  L P C .  V C L  F Q N
F G P C  I F N  F L V  K F V S  S R I
 L D P  V S S T  S L L  S L S  L P E L

TGAAGCTGTA AAGCTACAAA TAGTTCTTCA AATGGAACCC CAGATGCAGT  350
. S C K  A T N  S S S  N G T P  D A V
 E A V  K L Q I  V L Q  M E P  Q M Q S
  K L .  S Y K  . F F K  W N P  R C S
```

FIG 5 (continued)

```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
CCATGACTAA AATCTACCGT GGACCCCTGG ACCGGCCTGC TAGACTATGC   400
 H D .  N L P W  T P G  P A C  . T M L
  M T K  I Y R  G P L D  R P A  R L C
P . L K  S T V  D P W  T G L L  D Y A

TCTGATGTTA ATGACATTGA AGTCACCCCT CCCGAGGAAA TCTCAACTGC   450
  . C .  . H .  S H P S  R G N  L N C
S D V N  D I E  V T P  P E E I  S T A
 L M L  M T L K  S P L  P R K  S Q L H

ACAACCCCTA CTACACTCCA ATTCAGTAGG AAGCAGTTAG AGCAGTTGTC   500
T T P T  T L Q  F S R  K Q L E  Q L S
 Q P L  L H S N  S V G  S S .  S S C Q
  N P Y  Y T P  I Q .  E A V R  A V V

AGCCAACCTC CCCAACAGTA CTTGGGTTTT CCTGTTGAGA GGGTGGACTG   550
 A N L  P N S T  W V F  L L R  G W T E
  P T S  P T V  L G F S  C . E  G G L
S Q P P  Q Q Y  L G F  P V E R  V D .

AGAGACAGGA CTAGCTGGAT TTCCTAGGCT GACTAAGAAT CCCNAAGCCT   600
  R Q D  . L D  F L G .  L R I  P K P
R D R T  S W I  S . A  D . E S  X S L
 E T G  L A G F  P R L  T K N  P X A X

ANCTGGGAAG GTGACCGCAT CCATCTTTAA ACATGGGGCT TGCAACTTAG   650
X W E G  D R I  H L .  T W G L  Q L S
 X G K  V T A S  I F K  H G A  C N L A
  L G R  . P H  P S L N  M G L  A T .

CTCACACCCG ACCAATCAGA GAGCTCACTA AAATGCTAAT CAGGCAAAAA   700
 S H P  T N Q R  A H .  N A N  Q A K T
  H T R  P I R  E L T K  M L I  R Q K
L T P D  Q S E  S S L  K C .  S G K N
```

FIG 5 (continued)

```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
CAGGAGGTAA AGCAATAGCC AATCATCTAT TGCCTGAGAG CACAGCGGGA   750
  G G K   A I A   N H L L   P E S   T A G
Q E V K   Q . P   I I Y   C L R A   Q R E
 R R .   S N S Q   S S I   A . E   H S G K

AGGACAAGGA TTGGGATATA AACTCAGGCA TTCAAGCCAG CAACAGCAAC   800
R T R I   G I .   T Q A   F K P A   T A T
 G Q G   L G Y K   L R H   S S Q   Q Q Q P
  D K D   W D I   N S G I   Q A S   N S N

CCCCTTTGGG TCCCCTCCCA TTGTATGGGA GCTCTGTTTT CACTCTATTT   850
 P F G   S P P I   V W E   L C F   H S I S
  P L G   P L P   L Y G S   S V F   T L F
P L W V   P S H   C M G   A L F S   L Y F

CACTCTATTA AATCATGCAA CTGCACTCTT CTGGTCCGTG TTTTTTATGG   900
  L Y .   I M Q   L H S S   G P C   F L W
H S I K   S C N   C T L   L V R V   F Y G
 T L L   N H A T   A L F   W S V   F F M A

CTCAAGCTGA GCTTTTGTTC GCCATCCACC ACTGCTGTTT GCCACCGTCA   950
L K L S   F C S   P S T   T A V C   H R H
 S S .   A F V R   H P P   L L F   A T V T
  Q A E   L L F   A I H H   C C L   P P S

CAGACCCGCT GCTGACTTCC ATCCCTTTGG ATCCAGCAGA GTGTCCACTG   1000
 R P A   A D F H   P F G   S S R   V S T V
  D P L   L T S   I P L D   P A E   C P L
Q T R C   . L P   S L W   I Q Q S   V H C

TGCTCCTGAT CCAGCGAGGT ACCCATTGCC ACTCCCGATC AGGCTAAAGG   1050
  L L I   Q R G   T H C H   S R S   G . R
C S . S   S E V   P I A   T P D Q   A K G
 A P D   P A R Y   P L P   L P I   R L K A
```

FIG 5 (continued)

```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
CTTGCCATTG TTCCTGCATG GCTAAGTGCC TGGGTTTGTC CTAATAGAAC  1100
L A I V  P A W  L S A  W V C P  N R T
 L P L  F L H G  . V P  G F V  L I E L
  C H C  S C M  A K C L  G L S  . . N

TGAACACTGG TCACTGGGTT CCATGGTTCT CTTCCATGAC CCACGGCTTC  1150
 E H W  S L G S  M V L  F H D  P R L L
  N T G  H W V  P W F S  S M T  H G F
. T L V  T G F  H G S  L P .  P T A S

TAATAGAGCT ATAACACTCA CCGCATGGCC CAAGATTCCA TTCCTTGGTA  1200
  I E L  . H S  P H G P  R F H  S L V
. . S Y  N T H  R M A  Q D S I  P W Y
 N R A  I T L T  A W P  K I P  F L G I

TCTGTGAGGC CAAGAACCCC AGGTCAGAGA ANGTGAGGCT TGCCACCATT  1250
S V R P  R T P  G Q R  X . G L  P P F
 L . G  Q E P Q  V R E  X E A  C H H L
  C E A  K N P  R S E X  V R L  A T I

TGGGAAGTGG CCCACTGCCA TTTTGGTAGC GGCCCACCAC CATCTTGGGA  1300
 G K W  P T A I  L V A  A H H  H L G S
  G S G  P L P  F W .  R P T T  I L G
W E V A  H C H  F G S  G P P P  S W E

GCTGTGGGAG CAAGGATCCC CCAGTAACA                         1329
  C G S  K D P  P V T
A V G A  R I P  Q .
 L W E  Q G S P  S N
```

FIG 6

```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
CCTAGAACGT ATTCTGGAGA ATTGGGACCA ATGTGACACT CAGACGCTAA      50
P  R  T  Y  S  G  E  L  G  P  M  .  H  S  D  A  K
 L  E  R  I  L  E  N  W  D  Q  C  D  T  Q  T  L  R
  .  N  V  F  W  R  I  G  T  N  V  T  L  R  R  .

GAAAGAAACG ATTTATATTC TTCTGCAGTA CCGCCTGGCC ACAATATCCT     100
 K  E  T  I  Y  I  L  L  Q  Y  R  L  A  T  I  S  S
  K  K  R  F  I  F  F  C  S  T  A  W  P  Q  Y  P
E  R  N  D  L  Y  S  S  A  V  P  P  G  H  N  I  L

CTTCAAGGGA GAGAAACCTG GCTTCCTGAG GGAAGTATAA ATTATAACAT     150
  S  R  E  R  N  L  A  S  .  G  K  Y  K  L  .  H
L  Q  G  R  E  T  W  L  P  E  G  S  I  N  Y  N  I
 F  K  G  E  K  P  G  F  L  R  E  V  .  I  I  T  S

CATCTTACAG CTAGACCTCT TCTGTAGAAA GGAGGGCAAA TGGAGTGAAG     200
H  L  T  A  R  P  L  L  .  K  G  G  Q  M  E  .  S
 I  L  Q  L  D  L  F  C  R  K  E  G  K  W  S  E  V
  S  Y  S  .  T  S  S  V  E  R  R  A  N  G  V  K

TGCCATATGT GCAAACTTTC TTTTCATTAA GAGACAACTC ACAATTATGT     250
 A  I  C  A  N  F  L  F  I  K  R  Q  L  T  I  M  .
  P  Y  V  Q  T  F  F  S  L  R  D  N  S  Q  L  C
C  H  M  C  K  L  S  F  H  .  E  T  T  H  N  Y  V

AAAAAGTGTG GTTTATGCCC TACAGGAAGC CCTCAGAGTC CACCTCCCTA     300
  K  V  W  F  M  P  Y  R  K  P  S  E  S  T  S  L
K  K  C  G  L  C  P  T  G  S  P  Q  S  P  P  P  Y
 K  S  V  V  Y  A  L  Q  E  A  L  R  V  H  L  P  T

CCCCAGCGTC CCCTCCCCGA CTCCTTCCTC AACTAATAAG GACCCCCCTT     350
P  Q  R  P  L  P  D  S  F  L  N  .  .  G  P  P  F
 P  S  V  P  S  P  T  P  S  S  T  N  K  D  P  P  L
  P  A  S  P  P  R  L  L  P  Q  L  I  R  T  P  L

TAACCCAAAC GGTCCAAAAG GAGATAGACA AAGGGGTAAA CAATGAACCA     400
N  P  N  G  P  K  G  D  R  Q  R  G  K  Q  .  T  K
 T  Q  T  V  Q  K  E  I  D  K  G  V  N  N  E  P
.  P  K  R  S  K  R  R  .  T  K  G  .  T  M  N  Q

AAGAGTGCCA ATATTCCCCG ATTATGCCCC CTCCAAGCAG TGAGAGGAGG     450
  E  C  Q  Y  S  P  I  M  P  P  P  S  S  E  R  R
K  S  A  N  I  P  R  L  C  P  L  Q  A  V  R  G  G
 R  V  P  I  F  P  D  Y  A  P  S  K  Q  .  E  E  E

AGAATTCGGC CCAGCCAGAG TGCCTGTACC TTTTTCTCTC TCAGACTTAA     500
R  I  R  P  S  Q  S  A  C  T  F  F  S  L  R  L  K
 E  F  G  P  A  R  V  P  V  P  F  S  L  S  D  L  K
  N  S  A  Q  P  E  C  L  Y  L  F  L  S  Q  T  .
```

FIG 6 (continued)

```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
AGCAAATTAA AATAGACCTA GGTAAATTCT CAGATAACCC TGACGGCTAT   550
 A N . N R P R . I L R . P . R L Y
  Q I K I D L G K F S D N P D G Y
S K L K . T . V N S Q I T L T A I

ATTGATGTTT TACAAGGGTT AGGACAATCC TTTGATCTGA CATGGAGAGA   600
  . C F T R V R T I L . S D M E R
I D V L Q G L G Q S F D L T W R D
 L M F Y K G . D N P L I . H G E I

TATAATGTTA CTACTAAATC AGACACTAAC CCCAAATGAG AGAAGTGCCG   650
Y N V T T K S D T N P K . E K C R
 I M L L L N Q T L T P N E R S A A
  . C Y Y . I R H . P Q M R E V P

CTGTAACTGC AGCCCGAGAG TTTGGCGATC TTTGGTATCT CAGTCAGGCC   700
 C N C S P R V W R S L V S Q S G Q
  V T A A R E F G D L W Y L S Q A
L . L Q P E S L A I F G I S V R P

AACAATAGGA TGACAACAGA GGAAAGAACA ACTCCCACAG GCCAGCAGGC   750
  Q . D D N R G K N N S H R P A G
N N R M T T E E R T T P T G Q Q A
 T I G . Q Q R K E Q L P Q A S R Q

AGTTCCCAGT GTAGACCCTC ATTGGGACAC AGAATCAGAA CATGGAGATT   800
S S Q C R P S L G H R I R T W R L
 V P S V D P H W D T E S E H G D W
  F P V . T L I G T Q N Q N M E I

GGTGCCACAA ACATTTGCTA ACTTGCGTGC TAGAAGGACT GAGGAAAACT   850
 V P Q T F A N L R A R R T E E N .
  C H K H L L T C V L E G L R K T
G A T N I C . L A C . K D . G K L

AGGAAGAAGC CTATGAATTA CTCAATGATG TCCACTATAA CACAGGGAAA   900
  E E A Y E L L N D V H Y N T G K
R K K P M N Y S M M S T I T Q G K
 G R S L . I T Q . C P L . H R E R

GGAAGAAAAT CTTACTGCTT TTCTGGACAG ACTAAGGGAG GCATTGAGGA   950
G R K S Y C F S G Q T K G G I E E
 E E N L T A F L D R L R E A L R K
  K K I L L L F W T D . G R H . G

AGCATACCTC CCTGTCACCT GACTCTATTG AAGGCCAACT AATCTTAAAG  1000
 A Y L P V T . L Y . R P T N L K G
  H T S L S P D S I E G Q L I L K
S I P P C H L T L L K A N . S . R
```

FIG 6 (continued)

```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
GATAAGTTTA TCACTCAGTC AGCTGCAGAC ATTAGAAAAA ACTTCAAAAG  1050
  . V Y   H S V   S C R H   . K K   L Q K
D K F I   T Q S   A A D   I R K N   F K S
 I S L   S L S Q   L Q T   L E K   T S K V

TCTGCCTTAG GCCCGGAGCA GAACTTAGAA ACCCTATTTA ACTTGGCATC  1100
S A L G   P E Q   N L E   T L F N   L A S
 L P .   A R S R   T . K   P Y L   T W H P
  C L R   P G A   E L R N   P I .   L G I

CTCAGTTTTT TATAATAGAG ATCAGGAGGA GCAGGCGAAA CGGGACAAAC  1150
 S V F   Y N R D   Q E E   Q A K   R D K R
  Q F F   I I E   I R R S   R R N   G T N
L S F L   . . R   S G G   A G E T   G Q T

GGGATAAAAA AAAAAGGGGG GGTCCACTAC TTTAGTCATG GCCCTCAGGC  1200
  D K K   K R G   G P L L   . S W   P S G
G I K K   K G G   V H Y   F S H G   P Q A
 G . K   K K G G   S T T   L V M   A L R Q

AAGCAGACTT TGGAGGCTCT GCAAAAGGGA AAAGCTGGGC AAATCAAATG  1250
K Q T L   E A L   Q K G   K A G Q   I K C
 S R L   W R L C   K R E   K L G   K S N A
  A D F   G G S   A K G K   S W A   N Q M

CCTAATAGGG CTGGCTTCCA GTGCGGTCTA CAAGGACACT TTAAAAAAGA  1300
 L I G   L A S S   A V Y   K D T   L K K I
  . . G   W L P   V R S T   R T L   . K R
P N R A   G F Q   C G L   Q G H F   K K D

TTATCCAAGT AGAAATAAGC CGCCCCCTTG TCCATGCCCC TTACGTCAAG  1350
  I Q V   E I S   R P L V   H A P   Y V K
L S K .   K . A   A P L   S M P L   T S R
 Y P S   R N K P   P P C   P C P   L R Q G

GGAATCACTG GAAGCCCCAC TGCCCCAGGG GATGAAGATA CTCTGAGTCA  1400
G I T G   R P T   A P G   D E D T   L S Q
 E S L   E G P L   P Q G   M K I   L . V R
  N H W   K A H   C P R G   . R Y   S E S

GAAGCCATTA ACCAGATGAT CCAGCAGCAG GACTGAGGGT GCCCGGGGCG  1450
 K P L   T R .   S S R   T E G   A R G E
  S H .   P D D   P A A G   L R V   P G A
E A I N   Q M I   Q Q Q   D . G C   P G R

AGCGCCAGCC CATGCCATCA CCCTCACAGA GCCCCGGGTA TGTTTGACCA  1500
  R Q P   M P S   P S Q S   P G Y   V . P
S A S P   C H H   P H R   A P G M   F D H
 A P A   H A I T   L T E   P R V   C L T I
```

FIG 6 (continued)

```
         10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
TTGAGAGCCA A                                          1511
L  R  A
 .  E  P
 E  S  Q
```

FIG 7

```
          10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
ATGGGCAGCA GCCATCATCA TCATCATCAC AGCAGCGGCC TGGTGCCGCG      50
M G S S  H H H  H H H  S S G L  V P R

CGGCAGCCAT ATGGCTAGCA TGACTGGTGG ACAGCAAATG GGTCGGATCC     100
 G S H  M A S M  T G G  Q Q M  G R I L

TAGAACGTAT TCTGGAGAAT TGGGACCAAT GTGACACTCA GACGCTAAGA     150
  E R I  L E N  W D Q  C D T  Q T L R

AAGAAACGAT TTATATTCTT CTGCAGTACC GCCTGGCCAC AATATCCTCT     200
K K R F  I F F  C S T  A W P  Q Y P L

TCAAGGGAGA GAAACCTGGC TTCCTGAGGG AAGTATAAAT TATAACATCA     250
 Q G R  E T W  L P E  G S I  N Y N  I I

TCTTACAGCT AGACCTCTTC TGTAGAAAGG AGGGCAAATG GAGTGAAGTG     300
  L Q L  D L F  C R K  E G K  W S E  V

CCATATGTGC AAACTTTCTT TTCATTAAGA GACAACTCAC AATTATGTAA     350
P Y V Q  T F F  S L R  D N S  Q L C  K

AAAGTGTGGT TTATGCCCTA CAGGAAGCCC TCAGAGTCCA CCTCCCTACC     400
 K C G  L C P  T G S  P Q S  P P Y  P

CCAGCGTCCC CTCCCCGACT CCTTCCTCAA CTAATAAGGA CCCCCCTTTA     450
  S V P  S P T  P S S  T N K  D P P  L

ACCCAAACGG TCCAAAAGGA GATAGACAAA GGGGTAAACA ATGAACCAAA     500
T Q T V  Q K E  I D K  G V N  N E P  K

GAGTGCCAAT ATTCCCCGAT TATGCCCCCT CCAAGCAGTG AGAGGAGGAG     550
 S A N  I P R  L C P  L Q A  V R G  G E

AATTCGGCCC AGCCAGAGTG CCTGTACCTT TTTCTCTCTC AGACTTAAAG     600
  F G P  A R V  P V P  F S L  S D L  K

CAAATTAAAA TAGACCTAGG TAAATTCTCA GATAACCCTG ACGGCTATAT     650
Q I K I  D L G  K F S  D N P  D G Y  I

TGATGTTTTA CAAGGGTTAG GACAATCCTT TGATCTGACA TGGAGAGATA     700
 D V L  Q G L  G Q S  F D L  T W R  D I

TAATGTTACT ACTAAATCAG ACACTAACCC CAAATGAGAG AAGTGCCGCT     750
  M L L  L N Q  T L T  P N E  R S A  A

GTAACTGCAG CCCGAGAGTT TGGCGATCTT TGGTATCTCA GTCAGGCCAA     800
V T A A  R E F  G D L  W Y L  S Q A  N
```

FIG 7 (continued)

```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
CAATAGGATG ACAACAGAGG AAAGAACAAC TCCCACAGGC CAGCAGGCAG      850
 N  R  M   T  T  E  E   R  T  T   P  T  G   Q  Q  A  V

TTCCCAGTGT AGACCCTCAT TGGGACACAG AATCAGAACA TGGAGATTGG      900
 P  S  V   D  P  H  W   D  T  E   S  E  H   G  D  W

TGCCACAAAC ATTTGCTAAC TTGCGTGCTA GAAGGACTGA GGAAAACTAG      950
 C  H  K   H  L  L  T   C  V  L   E  G  L   R  K  T  R

GAAGAAGCCT ATGAATTACT CAATGATGTC CACTATAACA CAGGGAAAGG     1000
 K  K  P   M  N  Y  S   M  M  S   T  I  T   Q  G  K  E

AAGAAAATCT TACTGCTTTT CTGGACAGAC TAAGGGAGGC ATTGAGGAAG     1050
 E  N  L   T  A  F  L   D  R  L   R  E  A   L  R  K

CATACCTCCC TGTCACCTGA CTCTATTGAA GGCCAACTAA TCTTAAAGGA     1100
 H  T  S   L  S  P  D   S  I  E   G  Q  L   I  L  K  D

TAAGTTTATC ACTCAGTCAG CTGCAGACAT TAGAAAAAAC TTCAAAAGTC     1150
 K  F  I   T  Q  S  A   A  D  I   R  K  N   F  K  S  L

TGCCTAAGCT TGCGGCCGCA CTCGAGCACC ACCACCACCA CCACTGAGAT     1200
 P  K  L   A  A  A  L   E  H  H   H  H  H   H  .  D

CCGGCTGCTA ACAAAGCCCG AAAGGAAGCT GAGTTGGCTN GTGGCNA        1247
 P  A  A   N  K  A  R   K  E  A   E  L  A   X  G
```

FIG 8

```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
ATGGCTAGCA TGACTGGTGG ACAGCAAATG GGTCGGATCC TAGAACGTAT    50
M  A  S  M  T  G  G  Q  Q  M  G  R  I  L  E  R  I

TCTGGAGAAT TGGGACCAAT GTGACACTCA GACGCTAAGA AAGAAACGAT   100
 L  E  N  W  D  Q  C  D  T  Q  T  L  R  K  K  R  F

TTATATTCTT CTGCAGTACC GCCTGGCCAC AATATCCTCT TCAAGGGAGA   150
 I  F  F  C  S  T  A  W  P  Q  Y  P  L  Q  G  R

GAAACCTGGC TTCCTGAGGG AAGTATAAAT TATAACATCA TCTTACAGCT   200
E  T  W  L  P  E  G  S  I  N  Y  N  I  I  L  Q  L

AGACCTCTTC TGTAGAAAGG AGGGCAAATG GAGTGAAGTG CCATATGTGC   250
 D  L  F  C  R  K  E  G  K  W  S  E  V  P  Y  V  Q

AAACTTTCTT TTCATTAAGA GACAACTCAC AATTATGTAA AAAGTGTGGT   300
 T  F  F  S  L  R  D  N  S  Q  L  C  K  K  C  G

TTATGCCCTA CAGGAAGCCC TCAGAGTCCA CCTCCCTACC CCAGCGTCCC   350
L  C  P  T  G  S  P  Q  S  P  P  P  Y  P  S  V  P

CTCCCCGACT CCTTCCTCAA CTAATAAGGA CCCCCCTTTA ACCCAAACGG   400
 S  P  T  P  S  S  T  N  K  D  P  P  L  T  Q  T  V

TCCAAAAGGA GATAGACAAA GGGGTAAACA ATGAACCAAA GAGTGCCAAT   450
 Q  K  E  I  D  K  G  V  N  N  E  P  K  S  A  N

ATTCCCCGAT TATGCCCCCT CCAAGCAGTG AGAGGAGGAG AATTCGGCCC   500
I  P  R  L  C  P  L  Q  A  V  R  G  G  E  F  G  P

AGCCAGAGTG CCTGTACCTT TTTCTCTCTC AGACTTAAAG CAAATTAAAA   550
 A  R  V  P  V  P  F  S  L  S  D  L  K  Q  I  K  I

TAGACCTAGG TAAATTCTCA GATAACCCTG ACGGCTATAT TGATGTTTTA   600
 D  L  G  K  F  S  D  N  P  D  G  Y  I  D  V  L

CAAGGGTTAG GACAATCCTT TGATCTGACA TGGAGAGATA TAATGTTACT   650
Q  G  L  G  Q  S  F  D  L  T  W  R  D  I  M  L  L

ACTAAATCAG ACACTAACCC CAAATGAGAG AAGTGCCGCT GTAACTGCAG   700
 L  N  Q  T  L  T  P  N  E  R  S  A  A  V  T  A  A

CCCGAGAGTT TGGCGATCTT TGGTATCTCA GTCAGGCCAA CAATAGGATG   750
 R  E  F  G  D  L  W  Y  L  S  Q  A  N  N  R  M

ACAACAGAGG AAAGAACAAC TCCCACAGGC CAGCAGGCAG TTCCCAGTGT   800
T  T  E  E  R  T  T  P  T  G  Q  Q  A  V  P  S  V
```

FIG 8 (continued)

```
         10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
AGACCCTCAT TGGGACACAG AATCAGAACA TGGAGATTGG TGCCACAAAC   850
 D  P  H   W  D  T  E   S  E  H   G  D  W   C  H  K  H

ATTTGCTAAC TTGCGTGCTA GAAGGACTGA GGAAAACTAG GAAGAAGCCT   900
  L  L  T   C  V  L   E  G  L  R   K  T  R   K  K  P

ATGAATTACT CAATGATGTC CACTATAACA CAGGGAAAGG AAGAAAATCT   950
M  N  Y  S   M  M  S   T  I  T   Q  G  K  E   E  N  L

TACTGCTTTT CTGGACAGAC TAAGGGAGGC ATTGAGGAAG CATACCTCCC  1000
 T  A  F   L  D  R  L   R  E  A   L  R  K   H  T  S  L

TGTCACCTGA CTCTATTGAA GGCCAACTAA TCTTAAAGGA TAAGTTTATC  1050
  S  P  D   S  I  E   G  Q  L  I   L  K  D   K  F  I

ACTCAGTCAG CTGCAGACAT TAGAAAAAAC TTCAAAAGTC TGCCTAAGCT  1100
T  Q  S  A   A  D  I   R  K  N   F  K  S  L   P  K  L

TGCGGCCGCA CTCGAGCACC ACCACCACCA CCACTGAGAT CCGGCTGCTA  1150
 A  A  A   L  E  H  H   H  H  H   H  .  D   P  A  A  N

ACAAAGCCCG AAAGGAAGCT GAGTTGGCTG CTGCCA                 1186
  K  A  R   K  E  A   E  L  A  G   G
```

FIG 9

```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
TGTCCGCTGT GCTCCTGATC CAGCACAGGC GCCCATTGCC TCTCCCAATT   50
C P L C  S . S  S T G  A H C L  S Q L
 V R C  A P D P  A Q A  P I A  S P N W
  S A V  L L I  Q H R R  P L P  L P I

GGGCTAAAGG CTTGCCATTG TTCCTGCACA GCTAAGTGCC TGGGTTCATC  100
 G . R  L A I V  P A Q  L S A  W V H P
  A K G  L P L  F L H S  . V P  G F I
G L K A  C H C  S C T  A K C L  G S S

CTAATCGAGC TGAACACTAG TCACTGGGTT CCACGGTTCT CTTCCATGAC  150
  N R A  E H .  S L G S  T V L  F H D
L I E L  N T S  H W V  P R F S  S M T
 . S S  . T L V  T G F  H G S L  P . P

CCATGGCTTC TAATAGAGCT ATAACACTCA CTGCATGGTC CAAGATTCCA  200
P W L L  I E L  . H S  L H G P  R F H
 H G F  . . S Y  N T H  C M V  Q D S I
  M A S  N R A  I T L T  A W S  K I P

TTCCTTGGAA TCCGTGAGAC CAAGAACCCC AGGTCAGAGA ACACAAGGCT  250
 S L E  S V R P  R T P  G Q R  T Q G L
  P W N  P . D  Q E P Q  V R E  H K A
F L G I  R E T  K N P  R S E N  T R L

TGCCACCATG TTGGAAGCAG CCCACCACCA TTTTGGAAGC AGCCCGCCAC  300
  P P C  W K Q  P T T I  L E A  A R H
C H H V  G S S  P P P  F W K Q  P A T
 A T M  L E A A  H H H  F G S  S P P L

TATCTTGGGA GCTCTGGGAG CAAGGACCCC AGGTAACAAT TTGGTGACCA  350
Y L G S  S G S  K D P  R . Q F  G D H
 I L G  A L G A  R T P  G N N  L V T T
  S W E  L W E  Q G P Q  V T I  W . P

CGAAGGGACC TGAATCCGCA ACCATGAAGG GATCTCCAAA GCAATTGGAA  400
 E G T  . I R N  H E G  I S K  A I G N
  K G P  E S A  T M K G  S P K  Q L E
R R D L  N P Q  P . R  D L Q S  N W K
```

FIG 9 (continued)

```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
ATGTTCCTCC CAAGGCAAAA ATGCCCCTAA GATGTATTCT GGAGAATTGG   450
  V  P  P  K  A  K  M  P  L  R  C  I  L  E  N  W
M  F  L  P  R  Q  K  C  P  .  D  V  F  W  R  I  G
 C  S  S  Q  G  K  N  A  P  K  M  Y  S  G  E  L  G

GACCAATTTG ACCCTCAGAC AGTAAGAAAA AAATGACTTA TATTCTTCTG   500
D  Q  F  D  P  Q  T  V  R  K  K  .  L  I  F  F  C
 T  N  L  T  L  R  Q  .  E  K  N  D  L  Y  S  S  A
  P  I  .  P  S  D  S  K  K  K  M  T  Y  I  L  L

CAGTACCGCC CTGGCCACGA TATCCTCTTC AAGGGGGAGA AACCTGGCCT   550
 S  T  A  L  A  T  I  S  S  S  R  G  R  N  L  A  S
  V  P  P  W  P  R  Y  P  L  Q  G  G  E  T  W  P
Q  Y  R  P  G  H  D  I  L  F  K  G  E  K  P  G  L

CCTGAGGGAA GTATAAATTA TAACACCATC TTACAGCTAG ACCTGTTTTG   600
  .  G  K  Y  K  L  .  H  H  L  T  A  R  P  V  L
P  E  G  S  I  N  Y  N  T  I  L  Q  L  D  L  F  C
 L  R  E  V  .  I  I  T  P  S  Y  S  .  T  C  F  V

TAGAAAAGGA GGCAAATGGA GTGAAGTGCC ATATTTACAA ACTTTCTTTT   650
.  K  R  R  Q  M  E  .  S  A  I  F  T  N  F  L  F
 R  K  G  G  K  W  S  E  V  P  Y  L  Q  T  F  F  S
  E  K  E  A  N  G  V  K  C  H  I  Y  K  L  S  F

CATTAAAAGA CAACTCGCAA TTATGTTAAC AGTGTGATTT GTGTTCCTAC   700
 I  K  R  Q  L  A  I  M  L  T  V  .  F  V  F  L  H
  L  K  D  N  S  Q  L  C  .  Q  C  D  L  C  S  Y
H  .  K  T  T  R  N  Y  V  N  S  V  I  C  V  P  T

ACGGAAGCCC TCAGATTCTA CTCCCCACCC CCGGCATCTC CCCTGAATCC   750
  G  S  P  Q  I  L  L  P  T  P  G  I  S  P  E  S
T  E  A  L  R  F  Y  S  P  P  P  A  S  P  L  N  P
 R  K  P  S  D  S  T  P  H  P  R  H  L  P  .  I  P

CTCCCCAACT TATT                                         764
L  P  N  L
 S  P  T  Y
  P  Q  L  I
```

FIG 10

```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
TGTCCGCTGT GCTCCTGATC CAGCACAGGC GCCCATTGCC TCTCCCAATT      50
C P L C  S . S  S T G  A H C L  S Q L
 V R C  A P D P  A Q A  P I A  S P N W
  S A V  L L I  Q H R R  P L P  L P I

GGGCTAAAGG CTTGCCATTG TTCCTGCACA GCTAAGTGCC TGGGTTCATC     100
 G . R  L A I V  P A Q  L S A  W V H P
  A K G  L P L  F L H S  . V P  G F I
G L K A  C H C  S C T  A K C L  G S S

CTAATCGAGC TGAACACTAG TCACTGGGTT CCACGGTTCT CTTCCATGAC     150
  N R A  E H .  S L G S  T V L  F H D
L I E L  N T S  H W V  P R F S  S M T
 . S S  . T L V  T G F  H G S L  P . P

CCATGGCTTC TAATAGAGCT ATAACACTCA CTGCATGGTC CAAGATTCCA     200
P W L L  I E L  . H S  L H G P  R F H
 H G F  . . S Y  N T H  C M V  Q D S I
  M A S  N R A  I T L T  A W S  K I P

TTCCTTGGAA TCCGTGAGAC CAAGAACCCC AGGTCAGAGA ACACAAGGCT     250
 S L E  S V R P  R T P  G Q R  T Q G L
  P W N  P . D  Q E P Q  V R E  H K A
F L G I  R E T  K N P  R S E N  T R L

TGCCACCATG TTGGAAGCAG CCCACCACCA TTTTGGAAGC GGCCCGCCAC     300
  P P C  W K Q  P T T I  L E A  A R H
C H H V  G S S  P P P  F W K R  P A T
 A T M  L E A A  H H H  F G S  G P P L

TATCTTGGGA GCTCTGGGAG CAAGGACCCC CAGGTAACAA TTTGGTGACC     350
Y L G S  S G S  K D P  Q V T I  W . P
 I L G  A L G A  R T P  R . Q  F G D H
  S W E  L W E  Q G P P  G N N  L V T

ACGAAGGGAC CTGAATCCGC AACCATGAAG GGATCTCCAA AGCAATTGGA     400
 R R D  L N P Q  P . R  D L Q  S N W K
  E G T  . I R  N H E G  I S K  A I G
T K G P  E S A  T M K  G S P K  Q L E
```

FIG 10 (continued)

```
      10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
AATGTTCCTC CCAAGGCAAA AATGCCCCTA AGATGTATTC TGGAGAATTG   450
  C  S  S  Q  G  K  N  A  P  K  M  Y  S  G  E  L
N  V  P  P  K  A  K  M  P  L  R  C  I  L  E  N  W
 M  F  L  P  R  Q  K  C  P  .  D  V  F  W  R  I  G

GGACCAATCT GACCCTCAGA CAGTAAGAAA AAAAATGACT TATATTCTTC   500
G  P  I  .  P  S  D  S  K  K  K  N  D  L  Y  S  S
 D  Q  S  D  P  Q  T  V  R  K  K  M  T  Y  I  L  L
  T  N  L  T  L  R  Q  .  E  K  K  .  L  I  F  F

TGCAGTACCG CCTGGCCACG GATATCCTCT TCAAGGGGGA GAAACCTGGC   550
 A  V  P  P  G  H  G  Y  P  L  Q  G  G  E  T  W  P
  Q  Y  R  L  A  T  D  I  L  F  K  G  E  K  P  G
C  S  T  A  W  P  R  I  S  S  S  R  G  R  N  L  A

CTCCTGAGGG AAGTATAAAT TATAACACCA TCTTACAGCT AGACCTGTTT   600
  P  E  G  S  I  N  Y  N  T  I  L  Q  L  D  L  F
L  L  R  E  V  .  I  I  T  P  S  Y  S  .  T  C  F
 S  .  G  K  Y  K  L  .  H  H  L  T  A  R  P  V  L

TGTAGAAAAG GAGGCAAATG GAGTGAAGTG CCATATTTAC AAACTTTCTT   650
C  R  K  G  G  K  W  S  E  V  P  Y  L  Q  T  F  F
 V  E  K  E  A  N  G  V  K  C  H  I  Y  K  L  S  F
  .  K  R  R  Q  M  E  .  S  A  I  F  T  N  F  L

TTCATTAAAA GACAACTCGC AATTATGTAA ACAGTGTGAT TTGTGTCCTA   700
 S  L  K  D  N  S  Q  L  C  K  Q  C  D  L  C  P  T
  H  .  K  T  T  R  N  Y  V  N  S  V  I  C  V  L
F  I  K  R  Q  L  A  I  M  .  T  V  .  F  V  S  Y

CAGGAAGCCC TCAGATCTAC CTCCCTACCC CGGCATCTCC CTGACTCCTT   750
  G  S  P  Q  I  Y  L  P  T  P  A  S  P  .  L  L
Q  E  A  L  R  S  T  S  L  P  R  H  L  P  D  S  F
 R  K  P  S  D  L  P  P  Y  P  G  I  S  L  T  P  S

CCCCAACTAA TAAGGACCCA CTTCAGCCCA AACAGTCCAA AAGGACATAG   800
P  Q  L  I  R  T  H  F  S  P  N  S  P  K  G  H
 P  N  .  _  .  G  P  T  S  A  Q  T  V  Q  K  D  I
  P  T  N  K  D  P  L  Q  P  K  Q  S  K  R  T  .
```

FIG 11

```
      10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
GGCATTGATA GCACCCATCA GATGGCCAAA TCATTATTTA CTGGACCAGG      50
G I D S   T H Q   M A K   S L F T   G P G
 A L I   A P I R   W P N   H Y L   L D Q A
  H . .   H P S   D G Q I   I I Y   W T R

CCTTTTCAAA ACTATCAAGC AGATAGGGCC CGTGAAGCAT GCCAAAGAAA     100
 L F K   T I K Q   I G P   V K H   A K E I
  F S K   L S S   R . G P   . S M   P K K
P F Q N   Y Q A   D R A   R E A C   Q R N

TAATCCCCTG CCTTATCGCC ATGTTCCTTC AGGAGAACAA AGAACAGGCC     150
  I P C   L I A   M F L Q   E N K   E Q A
. S P A   L S P   C S F   R R T K   N R P
 N P L   P Y R H   V P S   G E Q   R T G H

ATTACCCAGG GGAAGACTGG CAACTAGATT TTACCCACAT GGCCAAATGT     200
I T Q G   K T G   N . I   L P T W   P N V
 L P R   G R L A   T R F   Y P H   G Q M S
  Y P G   E D W   Q L D F   T H M   A K C

CAGGGATTTC AGCATCTACT AGTCTGGGCA GATACTTTCA CTGGTTGGGT     250
 R D F   S I Y .   S G Q   I L S   L V G W
  G I S   A S T   S L G R   Y F H   W L G
Q G F Q   H L L   V W A   D T F T   G W V

GGAGTCTTCT CCTTGTAGGA CAGAAAAGAC CCAAGAGGTA ATAAAGGCAC     300
  S L L   L V G   Q K R P   K R .   . R H
G V F S   L . D   R K D   P R G N   K G T
 E S S   P C R T   E K T   Q E V   I K A L

TAATGAAATA ATTCCCAGAT TTGGACTTCC CCCAGGATTA CAGGGTGACA     350
. . N N   S Q I   W T S   P R I T   G . Q
 N E I   I P R F   G L P   P G L   Q G D N
  M K .   F P D   L D F P   Q D Y   R V T
```

FIG 11 (continued)

```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
ATGGCCCCGC TTTCAAGGCT GCAGTAACCC AGGGAGTATC CCAGGTGTTA   400
 W  P  R   F  Q  G  C   S  N  P   G  S  I   P  G  V  R
  G  P  A   F  K  A   A  V  T  Q   G  V  S   Q  V  L
M  A  P  L   S  R  L   Q  .  P   R  E  Y   P  R  C  .

GGCATACAAT ATCACTTACA CTGTGCCTGG AGGCCACAAT CCTCCAGAAA   450
  H  T  I   S  L  T   L  C  L  E   A  T  I   L  Q  K
G  I  Q  Y   H  L  H   C  A  W   R  P  Q  S   S  R  K
 A  Y  N   I  T  Y  T   V  P  G   G  H  N   P  P  E  K

AGTCAAGAAA ATGAATGAAA CACTCAAAGA TCTAAAAAAG CTAACCCAAG   500
S  Q  E  N   E  .  N   T  Q  R   S  K  K  A   N  P  R
 V  K  K   M  N  E  T   L  K  D   L  K  K   L  T  Q  E
  S  R  K   .  M  K  H   S  K  I   .  K  S   .  P  K

AAACCCACAT TGCATGACCT GTTCTGTTGC CTATAACCTT ACTAAGAATC   550
 N  P  H   C  M  T  C   S  V  A   Y  N  L   T  K  N  P
  T  H  I   A  .  P  V   L  L  P   I  T  L   L  R  I
K  P  T  L   H  D  L   F  C  C   L  .  P   Y  .  E  S

CATAACTATC CCCCAAAAAG CAGGACTTAG CCCATACGAG ATGCTATATG   600
  .  L  S   P  K  K   Q  D  L  A   H  T  R   C  Y  M
H  N  Y  P   P  K  S   R  T  .   P  I  R   D  A  I  W
 I  T  I   P  Q  K  A   G  L  S   P  Y  E   M  L  Y  G

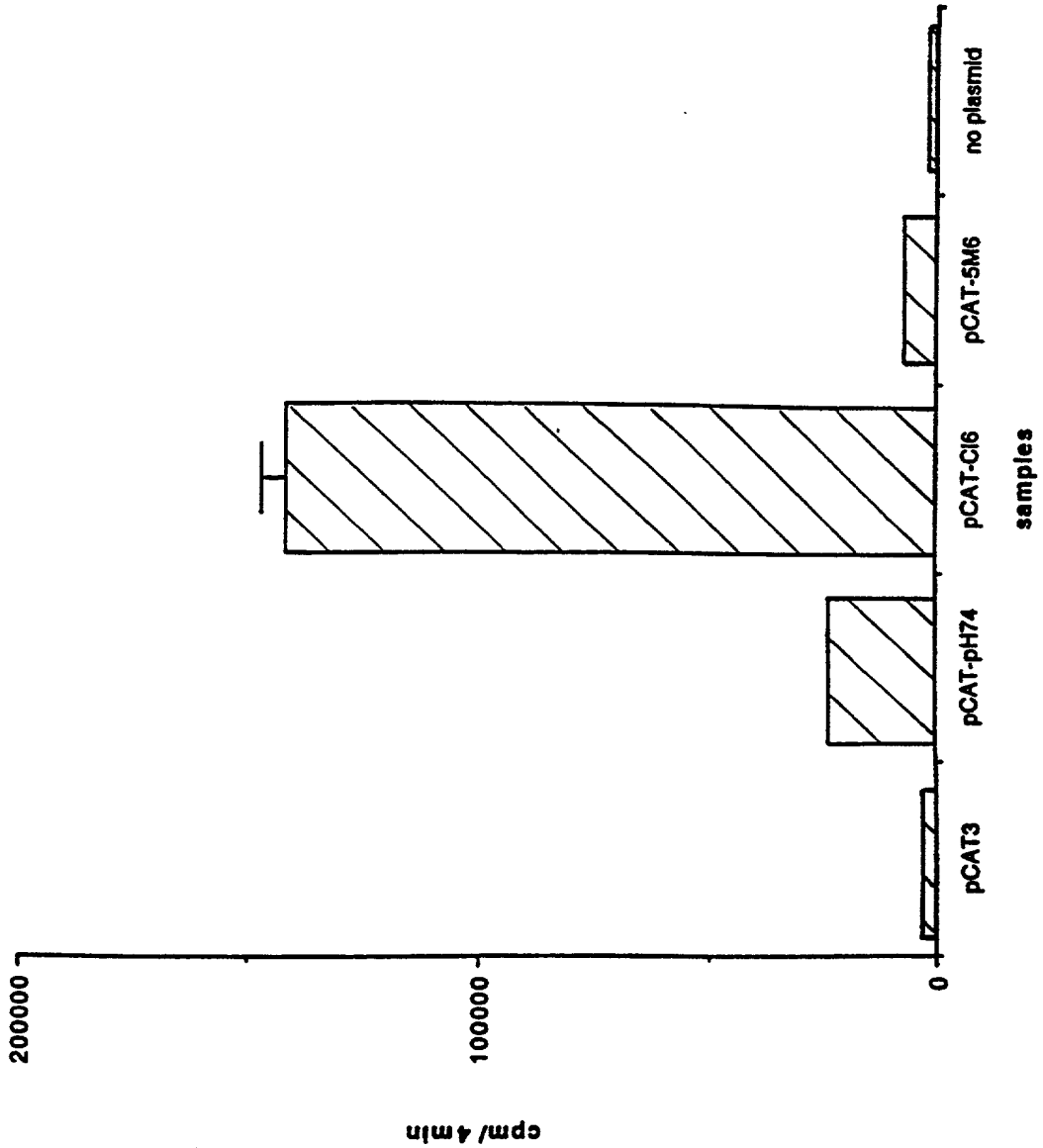
GATGGCCTTT CCTAACCAAT GACCTTGTGC TTGACTGAGA AATGGCCAAC   650
D  G  L  S   .  P  M   T  L  C   L  T  E  K   W  P  T
 M  A  F   P  N  Q  .   P  C  A   .  L  R  N   G  Q  L
  W  P  F   L  T  N   D  L  V  L   D  .  E   M  A  N

TTAGTTGCAG ACATCACCTC CTTAGCCAAA TATCAACAAG TTCTTAAAAC   700
 .  L  Q   T  S  P  P   .  P  N   I  N  K   F  L  K  H
  S  C  R   H  H  L   L  S  Q  I   S  T  S   S  .  N
L  V  A  D   I  T  S   L  A  K   Y  Q  Q  V   L  K  T
```

FIG 11 (continued)

```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
ATCACAGGGA ACCTGTCCCC GAGAGGAGGG AAAGGAACTA TTCCACCCTG      750
  H R E  P V P  E R R E  R N Y  S T L
I T G N  L S P  R G G  K G T I  P P W
 S Q G  T C P R  E E G  K E L  F H P G

GTGACATG                                                   758
V  T
 .  H
  D  M
```


200000
100000
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cpm/ 4min
pCAT3
pCAT-pH74
pCAT-CI6
pCAT-SM6
no plasmid
samples

FIG 12

FIG13

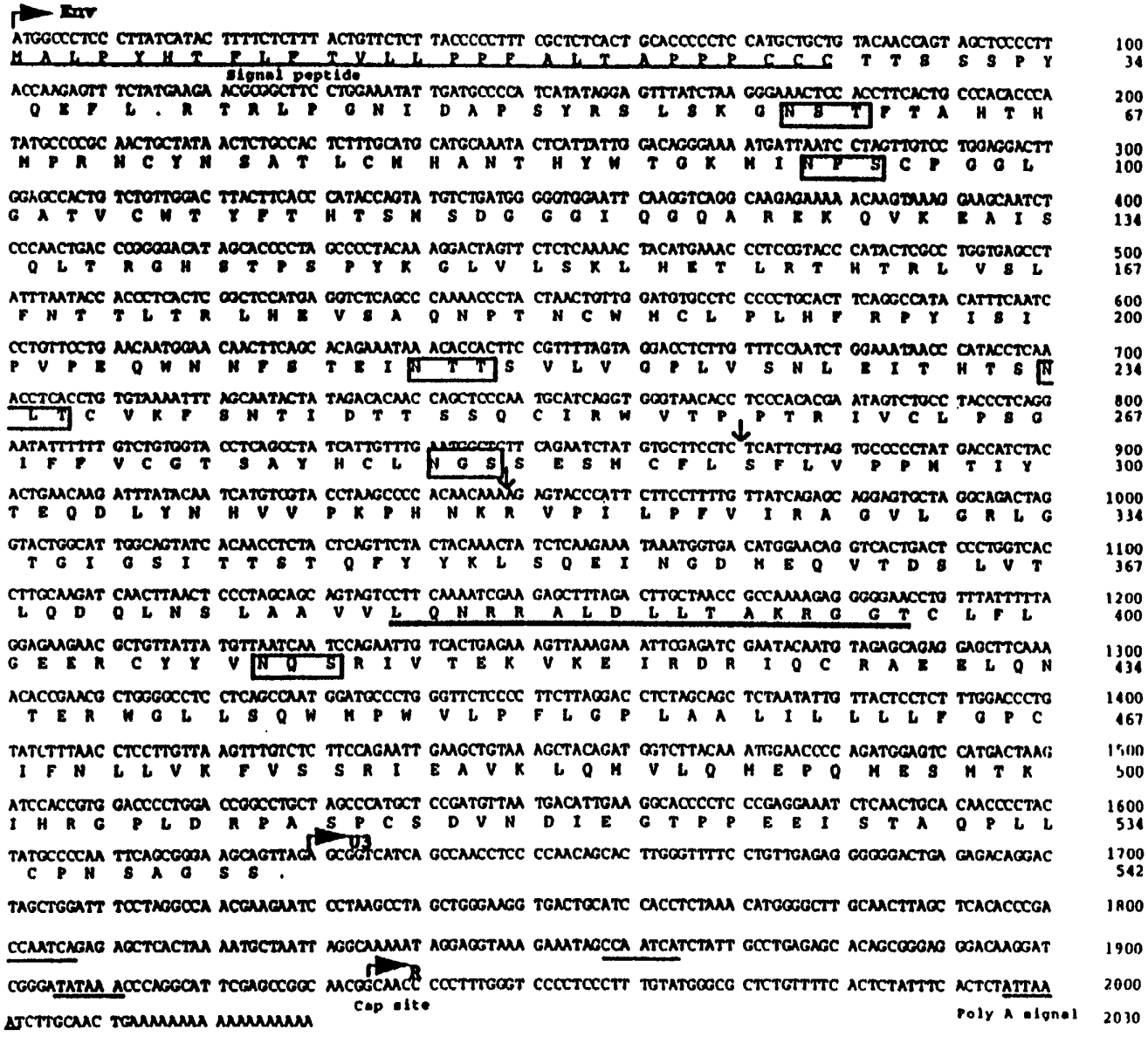

FIG 14

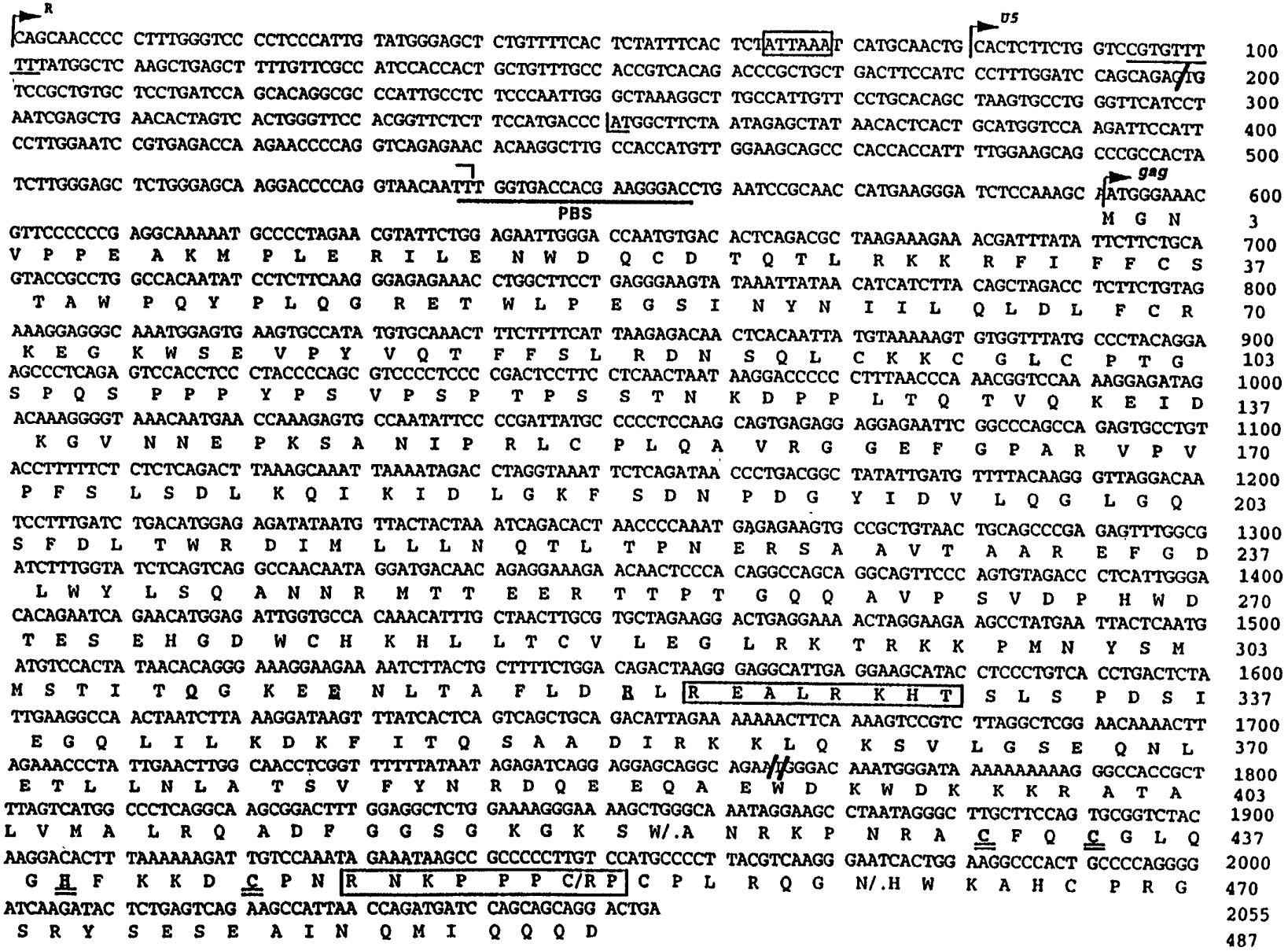

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FIG 15

```
GGACCCGTAG TATGGGGTAA TCCCCTCCGG GAAACCAAGC CCCAGTACTC AGAAGAAGAA ATAGAATGGG GAACCTCACG AGGACATGGT TTCCTCCCCT   100
G P V V W G N P L R E T K P Q Y S E E E I E W G T S R G H G F L P S                                                34

CAGGATGGCT AGCCACTGAA GAAGGAAAAA TACTTTTGCT GGCAGCTAAC CAATGGAAAT TACTTAAAAC CCTTCAGCAA ACCTTCCACT TAGGCATTGA   200
 G W L A T E E G K I L L L A A N Q W K L L K T L Q Q T F H L G I D                                                67

TAGCACCCAT CAGATAGCCA AATCATTATT TACTGGACCA GGCCTTTTCA AAACTATCAA GCAGATAGTC AGGGCCTGTG AAGTGTGCCA AAGAAATAAT   300
 S T H Q I A K S L F T G P G L F K T I K Q I V R A C E V C Q R N N                                                100

CCCCTGCCTT ATCGCCAAGC TCCTTCAGGA GAACAAAGAA CAGGCAATTA CCCAAGAGAA GACTGGCAAC TAGATTTTAT CCACATGCCA AAATCACAGG   400
P L P Y R Q A P S G E Q R T G N Y P R E D W Q L D F I H M P K S Q G                                                134

GATTTCAGTG TCTACTAGTC TGGGTAGATA CTTTCACTGG TTGGGCAGAG GCCTTCCCCT GTAGGACAGA AAAGTTCCAA GAGGTAATAA AGGCACTAGT   500
 F Q C L L V W V D T F T G W A E A P P C R T E K F Q E V I K A L V                                                167

TCATGAAGTA ATTCCCAGAT TCGGACTTCC CTGAGGCTTA CAGAGTGACA ATGGTCCTGC TTTCAAGGCC ACAGTAACCC AGGGAGTATC CCAGGCGTTA   600
 H E V I P R F G L P . G L Q S D N G P A F K A T V T Q G V S Q A L                                                200

GGTATAGAAT ATCACTTACA CTGCACCTAG AGGCCACAAT CCTCAGGGAA GGTTGAGAAA ATGAA//ACAC TCAAACGACA TCTAAACAAG CTAACCCAGG   700
G I E Y H L H C T . R P Q S S G K V E K M K T L K R H L N K L T Q E                                                234

AAACCCACCT CGCATGGTCT GCTCTGTTGT CTATAGCCTT ACTAAGAATC CAAAACTCTC CCCAAAAGGC AGGACTTAGC CCATACAGAA TGCTGTATGG   800
 T H L A W S A L L S I A L L R I Q N S P Q K A G L S P Y R M L Y G                                                267

ACGGTCCTTC CTAACCAATG ACCTTCTGCT TGACCAAGAG ATGGCCAACT TAGTTGCAGA CATCACCTCC TTAGCCAAAT ATCAACAAGT TCTTAAAACA   900
 R S F L T N D L L L D Q E M A N L V A D I T S L A K Y Q Q V L K T                                                300

TTACAAGGAG CCTGTCCCCG AGAGGAGGGA AAAGAAATAT TCCACCCTGG TGTCATGGTA TTAGTCAAGT CCCTTCCCTC TAATTCCCCA TCCCTAGACA  1000
L Q G A C P R E E G K E I F H P G V M V L V K S L P S M S P S L D T                                                334

CATCCTGGGG AGGACCCTAC CCAGTCATTT TATCTATCCC AACTGCGGTT AAAGTGGCTG GAGTGGAGTC TTGGATACAT CACACTCGAA TCAAACCCTG  1100
 S W G G P Y P V I L S I P T A V K V A G V E S W I H H T R I K P W                                                367

GATACTGCCG AAGGAACCCG AAAATCCAGG GGACAACGCT AGCTATTTCT TTGAACCTCT AGAGGATCTG TGCCTGCTCT TCAAGCAACA ACCGTGA     1197
 I L P K E P E N P G D N A S Y F F E P L E D L C L L F K Q Q P .                                                  398
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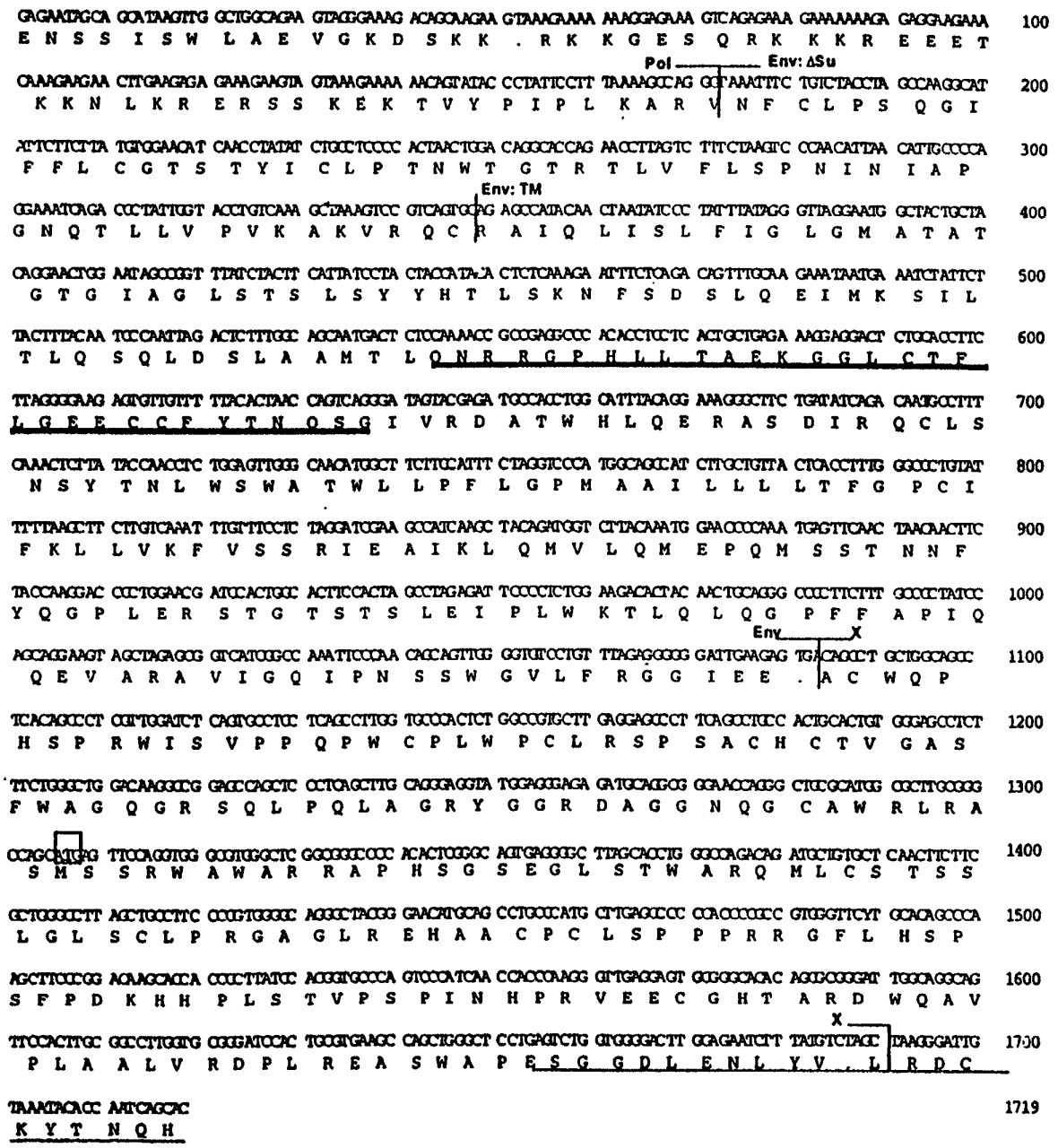
09/319156

FIG 16



Docket No.: 103514

DECLARATION AND POWER OF ATTORNEY UNDER 35 USC §371(c)(4) FOR PCT APPLICATION FOR UNITED STATES PATENT

As a below named inventor, I hereby declare that:
my residence, post office address and citizenship are as stated below under my name;

I verily believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought, namely the invention entitled: RETROVIRAL NUCLEIC MATERIAL AND NUCLEOTIDE FRAGMENTS, IN PARTICULAR ASSOCIATED WITH MULTIPLE SCLEROSIS AND/OR RHEUMATOID ARTHRITIS, FOR DIAGNOSTIC, PROPHYLACTIC AND THERAPEUTIC USES described and claimed in international application number PCT/FR98/01460 filed July 7, 1998 .

I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations §1.56.

Under Title 35, U.S. Code §119, the priority benefits of the following foreign application(s) filed within one year prior to my international application are hereby claimed:

French Patent Application No. 97 08816 filed July 7, 1997

The following application(s) for patent or inventor's certificate on this invention were filed in countries foreign to the United States of America either (a) more than one year prior to my international application, or (b) before the filing date of the above-named foreign priority application(s):

I hereby appoint the following as my attorneys of record with full power of substitution and revocation to prosecute this application and to transact all business in the Patent Office:

James A. Oliff, Reg. No. 27,075; William P. Berridge, Reg. No. 30,024;
Kirk M. Hudson, Reg. No. 27,562; Thomas J. Pardini, Reg. No. 30,411;
Edward P. Walker, Reg. No. 31,450; Robert A. Miller, Reg. No. 32,771;
Mario A. Costantino, Reg. No. 33,565; and Caroline D. Dennison, Reg. No. 34,494.

ALL CORRESPONDENCE IN CONNECTION WITH THIS APPLICATION SHOULD BE SENT TO OLIFF & BERRIDGE, PLC, P.O. BOX 19928, ALEXANDRIA, VIRGINIA 22320, TELEPHONE (703) 836-6400.

I hereby declare that I have reviewed and understand the contents of this Declaration, and that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-00

1 ***Typewritten Full Name of Sole or First Inventor***

Given Name	Middle Initial	Family Name
Glaucia		PARANHOS-BACCALA

2 **Inventor's Signature** Glaucia Paranhos Baccala

3 **Date of Signature**

Month	Day	Year
June	28	1999

Residence: Lyon (City) — State or Province — FRANCE (Country) FRX

Citizenship: BRASIL

Post Office Address: 75 Cours Gambetta
(Insert complete mailing address, including country) 69003 Lyon FRANCE

Note to Inventor: Please sign name on line 2 exactly as it appears in line 1 and insert the actual date of signing on line 3.

IF THERE IS MORE THAN ONE INVENTOR USE PAGE 2 AND PLACE AN "X" HERE ☒
(Discard this page in a sole inventor application)

2-00

1 ***Typewritten Full Name of Joint Inventor*** Florence (Given Name) | Middle Initial | KOMURIAN-PRADEL (Family Name)

2 **Inventor's Signature:** Florence PRADEL

3 **Date of Signature:** 21 JUIN 1999 (Month / Day / Year)

Residence: Poleymieux Au Mont D'Or (City) | (State or Province) | FRANCE (Country) JRX

Citizenship: FRANCE

Post Office Address: (Insert complete mailing address, including country) 114 Chemin du Pavillon, 69250 Poleymieux Au Mont D'Or FRANCE

3-00

1 ***Typewritten Full Name of Joint Inventor*** Frederic (Given Name) | Middle Initial | BEDIN (Family Name)

2 **Inventor's Signature:** Frederic BEDIN

3 **Date of Signature:** 30 JUIN 1999 (Month / Day / Year)

Residence: Lyon (City) | (State or Province) | FRANCE (Country) JRX

Citizenship: FRANCE

Post Office Address: (Insert complete mailing address, including country) 6 Rue Gaspard Andre, 69002 Lyon FRANCE

4-00

1 ***Typewritten Full Name of Joint Inventor*** Mireille (Given Name) | Middle Initial | SODOYER (Family Name)

2 **Inventor's Signature:** Mireille SODOYER

3 **Date of Signature:** 30 JUIN 1999 (Month / Day / Year)

Residence: Sainte Foy Les Lyon (City) | (State or Province) | FRANCE (Country) JRX

Citizenship: FRANCE

Post Office Address: (Insert complete mailing address, including country) 5 rue du Brulet, 69110 Sainte Foy Les Lyon FRANCE

5-00

1 ***Typewritten Full Name of Joint Inventor*** Catherine (Given Name) | Middle Initial | OTT (Family Name)

2 **Inventor's Signature:** Catherine OTT

3 **Date of Signature:** 30 JUIN 1999 (Month / Day / Year)

Residence: Lyon (City) | (State or Province) | FRANCE (Country) FRX

Citizenship: FRANCE

Post Office Address: (Insert complete mailing address, including country) 103 Avenue Berthelot, 69007 Lyon FRANCE

Note to Inventor: Please sign name on line 2 exactly as it appears in line 1 and insert the actual date of signing on line 3.

This form may be executed only when attached to the first page of the Declaration and Power of Attorney of the application to which it pertains.

IF THERE IS MORE THAN ONE INVENTOR USE PAGE 2 AND PLACE AN "X" HERE ☒
(Discard this page in a sole inventor application)

6-00

1 ***Typewritten Full Name of Joint Inventor***

François		MALLET
Given Name	Middle Initial	Family Name

2 **Inventor's Signature:** François MALLET Mallet

3 **Date of Signature:** 30 Juin 1999

Month	Day	Year

Residence: Villeurbanne / FRANCE FRX
City / State or Province / Country

Citizenship: FRANCE

Post Office Address: 84 rue Anatole France
(Insert complete mailing address, including country) 69100 Villeurbanne FRANCE

7-00

1 ***Typewritten Full Name of Joint Inventor***

Herve		PERRON
Given Name	Middle Initial	Family Name

2 **Inventor's Signature:** Herve Jean-François PERRON

3 **Date of Signature:** 9 Août 1999

Month	Day	Year

Residence: Lyon / FRANCE FRX
City / State or Province / Country

Citizenship: FRANCE

Post Office Address: 15 rue de Boyer
(Insert complete mailing address, including country) 69005 Lyon FRANCE

8-00

1 ***Typewritten Full Name of Joint Inventor***

Bernard	F.	MANDRAND
Given Name	Middle Initial	Family Name

2 **Inventor's Signature:** Bernard F. Mandrand

3 **Date of Signature:** 30 Juin 1999.

Month	Day	Year

Residence: Villeurbanne / FRANCE FRX
City / State or Province / Country

Citizenship: FRANCE

Post Office Address: 21 rue de la Doua
(Insert complete mailing address, including country) 69100 Villeurbanne FRANCE

1 ***Typewritten Full Name of Joint Inventor***

Given Name	Middle Initial	Family Name

2 **Inventor's Signature:**

3 **Date of Signature:**

Month	Day	Year

Residence:
City / State or Province / Country

Citizenship:

Post Office Address:
(Insert complete mailing address, including country)

Note to Inventor: Please sign name on line 2 exactly as it appears in line 1 and insert the actual date of signing on line 3.

This form may be executed only when attached to the first page of the Declaration and Power of Attorney of the application to which it pertains.

SEQUENCE LISTING

(2) INFORMATION FOR SEQ ID NO: 68:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 34 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 68:

GACTCGCTGC AGATCGATTT TTTTTTTTTT TTTT 34

(2) INFORMATION FOR SEQ ID NO: 69:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 69:

GCCATCAAGC CACCCAAGAA CTCTTAACTT 30

(2) INFORMATION FOR SEQ ID NO: 70:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 70:

CCAATAGCCA GACCATTATA TACACTAATT 30

(2) INFORMATION FOR SEQ ID NO: 112:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 310 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 112:

```
GCTTATAGAA GGACCCCTAG TATGGGGTAA TCCCCTCTGG GAAACCAAGC CCCAGTACTC   60
AGCAGGAAAA ATAGAATAGG AAACCTCACA AGGACATACT TTCCTCCCCT CCAGATGGCT  120
AGCCACTGAG GAAGGAAAAA TACTTTCACC TGCAGCTAAC CAACAGAAAT TACTTAAAAC  180
CCTTCACCAA ACCTTCCACT TAGGCATTGA TAGCACCCAT CAGATGGCCA AATTATTATT  240
TACTGGACCA GGCCTTTTCA AAACTATCAA GAAGATAGTC AGGGGCTGTG AAGTGTGCCA  300
AAGAAATAAT                                                         310
```

(2) INFORMATION FOR SEQ ID NO: 113:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 103 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 113:

```
Leu Ile Glu Gly Pro Leu Val Trp Gly Asn Pro Leu Trp Glu Thr Lys
1               5                  10                  15
Pro Gln Tyr Ser Ala Gly Lys Ile Glu Xaa Glu Thr Ser Gln Gly His
            20                  25                  30
Thr Phe Leu Pro Ser Arg Trp Leu Ala Thr Glu Glu Gly Lys Ile Leu
        35                  40                  45
Ser Pro Ala Ala Asn Gln Gln Lys Leu Leu Lys Thr Leu His Gln Thr
    50                  55                  60
Phe His Leu Gly Ile Asp Ser Thr His Gln Met Ala Lys Leu Leu Phe
65                  70                  75                  80
Thr Gly Pro Gly Leu Phe Lys Thr Ile Lys Lys Ile Val Arg Gly Cys
                85                  90                  95
Glu Val Cys Gln Arg Asn Asn
            100
```

(2) INFORMATION FOR SEQ ID NO: 114:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 635 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 114:

```
CCCTGTATCT TTAACCTCCT TGTTAAGTTT GTCTCTTCCA GAATCAAAAC TGTAAAACTA   60
CAAATTGTTC TTCAAATGGA GCACCAGATG GAGTCCATGA CTAAGATCCA CCGTGGACCC  120
CTGGACCGGC CTGCTAGCCC ATGCTCCGAT GTTAATGACA TTGAAGGCAC CCCTCCCGAG  180
GAAATCTCAA CTGCACAACC CCTACTATGC CCCAATTCAG CGGGAAGCAG TTAGAGCGGT  240
CATCAGCCAA CCTCCCCAAC AGCACTTGGG TTTTCCTGTT GAGAGGGGGG ACTGAGAGAC  300
AGGACTAGCT GGATTTCCTA GGCCAACGAA GAATCCCTAA GCCTAGCTGG GAAGGTGACT  360
GCATCCACCT CTAAACATGG GGCTTGCAAC TTAGCTCACA CCCGACCAAT CAGAGAGCTC  420
ACTAAAATGC TAATTAGGCA AAAATAGGAG GTAAAGAAAT AGCCAATCAT CTATTGCCTG  480
AGAGCACAGC GGGAGGGACA AGGATCGGGA TATAAACCCA GGCATTCGAG CCGGCAACGG  540
CAACCCCCTT TGGGTCCCCT CCCTTTGTAT GGGCGCTCTG TTTTCACTCT ATTTCACTCT  600
ATTAAATCTT GCAACTGAAA AAAAAAAAAA AAAAA                              635
```

(2) INFORMATION FOR SEQ ID NO: 115

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 77 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 115:

```
Pro Cys Ile Phe Asn Leu Leu Val Lys Phe Val Ser Ser Arg Ile Lys
1               5                  10                  15
Thr Val Lys Leu Gln Ile Val Leu Gln Met Glu His Gln Met Glu Ser
            20                  25                  30
Met Thr Lys Ile His Arg Gly Pro Leu Asp Arg Pro Ala Ser Pro Cys
        35                  40                  45
Ser Asp Val Asn Asp Ile Glu Gly Thr Pro Pro Glu Glu Ile Ser Thr
    50                  55                  60
Ala Gln Pro Leu Leu Cys Pro Asn Ser Ala Gly Ser Ser
65                  70                  75
```

(2) INFORMATION FOR SEQ ID NO: 116:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 32 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 116:

TGGGGTTCCA TTTGTAAGAC CATCTGTAGC TT 32

(2) INFORMATION FOR SEQ ID NO: 117:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1481 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 117:

ATGGCCCTCC CTTATCATAC TTTTCTCTTT ACTGTTCTCT TACCCCCTTT CGCTCTCACT 60
GCACCCCCTC CATGCTGCTG TACAACCAGT AGCTCCCCTT ACCAAGAGTT TCTATGAAGA 120
ACGCGGCTTC CTGGAAATAT TGATGCCCCA TCATATAGGA GTTTATCTAA GGGAAACTCC 180
ACCTTCACTG CCCACACCCA TATGCCCCGC AACTGCTATA ACTCTGCCAC TCTTTGCATG 240
CATGCAAATA CTCATTATTG GACAGGGAAA ATGATTAATC CTAGTTGTCC TGGAGGACTT 300
GGAGCCACTG TCTGTTGGAC TTACTTCACC CATACCAGTA TGTCTGATGG GGGTGGAATT 360
CAAGGTCAGG CAAGAGAAAA ACAAGTAAAG GAAGCAATCT CCCAACTGAC CCGGGGACAT 420
AGCACCCCTA GCCCCTACAA AGGACTAGTT CTCTCAAAAC TACATGAAAC CCTCCGTACC 480
CATACTCGCC TGGTGAGCCT ATTTAATACC ACCCTCACTC GGCTCCATGA GGTCTCAGCC 540
CAAAACCCTA CTAACTGTTG GATGTGCCTC CCCCTGCACT TCAGGCCATA CATTTCAATC 600
CCTGTTCCTG AACAATGGAA CAACTTCAGC ACAGAAATAA ACACCACTTC CGTTTTAGTA 660
GGACCTCTTG TTTCCAATCT GGAAATAACC CATACCTCAA ACCTCACCTG TGTAAAATTT 720
AGCAATACTA TAGACACAAC CAGCTCCCAA TGCATCAGGT GGGTAACACC TCCCACACGA 780
ATAGTCTGCC TACCCTCAGG AATATTTTTT GTCTGTGGTA CCTCAGCCTA TCATTGTTTG 840
AATGGCTCTT CAGAATCTAT GTGCTTCCTC TCATTCTTAG TGCCCCCTAT GACCATCTAC 900
ACTGAACAAG ATTTATACAA TCATGTCGTA CCTAAGCCCC ACAACAAAAG AGTACCCATT 960
CTTCCTTTTG TTATCAGAGC AGGAGTGCTA GGCAGACTAG GTACTGGCAT TGGCAGTATC 1020

ACAACCTCTA CTCAGTTCTA CTACAAACTA TCTCAAGAAA TAAATGGTGA CATGGAACAG 1080
GTCACTGACT CCCTGGTCAC CTTGCAAGAT CAACTTAACT CCCTAGCAGC AGTAGTCCTT 1140
CAAAATCGAA GAGCTTTAGA CTTGCTAACC GCCAAAAGAG GGGGAACCTG TTTATTTTTA 1200
GGAGAAGAAC GCTGTTATTA TGTTAATCAA TCCAGAATTG TCACTGAGAA AGTTAAAGAA 1260
ATTCGAGATC GAATACAATG TAGAGCAGAG GAGCTTCAAA ACACCGAACG CTGGGGCCTC 1320
CTCAGCCAAT GGATGCCCTG GGTTCTCCCC TTCTTAGGAC CTCTAGCAGC TCTAATATTG 1380
TTACTCCTCT TTGGACCCTG TATCTTTAAC CTCCTTGTTA AGTTTGTCTC TTCCAGAATT 1440
GAAGCTGTAA AGCTACAGAT GGTCTTACAA ATGGAACCCC A 1481

(2) INFORMATION FOR SEQ ID NO: 118:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 493 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 118:

Met Ala Leu Pro Tyr His Thr Phe Leu Phe Thr Val Leu Leu Pro Pro
1 5 10 15
Phe Ala Leu Thr Ala Pro Pro Pro Cys Cys Cys Thr Thr Ser Ser Ser
20 25 30
Pro Tyr Gln Glu Phe Leu Xaa Arg Thr Arg Leu Pro Gly Asn Ile Asp
35 40 45
Ala Pro Ser Tyr Arg Ser Leu Ser Lys Gly Asn Ser Thr Phe Thr Ala
50 55 60
His Thr His Met Pro Arg Asn Cys Tyr Asn Ser Ala Thr Leu Cys Met
65 70 75 80
His Ala Asn Thr His Tyr Trp Thr Gly Lys Met Ile Asn Pro Ser Cys
85 90 95
Pro Gly Gly Leu Gly Ala Thr Val Cys Trp Thr Tyr Phe Thr His Thr
100 105 110
Ser Met Ser Asp Gly Gly Gly Ile Gln Gly Gln Ala Arg Glu Lys Gln
115 120 125
Val Lys Glu Ala Ile Ser Gln Leu Thr Arg Gly His Ser Thr Pro Ser
130 135 140
Pro Tyr Lys Gly Leu Val Leu Ser Lys Leu His Glu Thr Leu Arg Thr

```
145                 150                 155                 160
His Thr Arg Leu Val Ser Leu Phe Asn Thr Thr Leu Thr Arg Leu His
                165                 170                 175
Glu Val Ser Ala Gln Asn Pro Thr Asn Cys Trp Met Cys Leu Pro Leu
            180                 185                 190
His Phe Arg Pro Tyr Ile Ser Ile Pro Val Pro Glu Gln Trp Asn Asn
        195                 200                 205
Phe Ser Thr Glu Ile Asn Thr Thr Ser Val Leu Val Gly Pro Leu Val
    210                 215                 220
Ser Asn Leu Glu Ile Thr His Thr Ser Asn Leu Thr Cys Val Lys Phe
225                 230                 235                 240
Ser Asn Thr Ile Asp Thr Thr Ser Ser Gln Cys Ile Arg Trp Val Thr
                245                 250                 255
Pro Pro Thr Arg Ile Val Cys Leu Pro Ser Gly Ile Phe Phe Val Cys
            260                 265                 270
Gly Thr Ser Ala Tyr His Cys Leu Asn Gly Ser Ser Glu Ser Met Cys
        275                 280                 285
Phe Leu Ser Phe Leu Val Pro Pro Met Thr Ile Tyr Thr Glu Gln Asp
    290                 295                 300
Leu Tyr Asn His Val Val Pro Lys Pro His Asn Lys Arg Val Pro Ile
305                 310                 315                 320
Leu Pro Phe Val Ile Arg Ala Gly Val Leu Gly Arg Leu Gly Thr Gly
                325                 330                 335
Ile Gly Ser Ile Thr Thr Ser Thr Gln Phe Tyr Tyr Lys Leu Ser Gln
            340                 345                 350
Glu Ile Asn Gly Asp Met Glu Gln Val Thr Asp Ser Leu Val Thr Leu
        355                 360                 365
Gln Asp Gln Leu Asn Ser Leu Ala Ala Val Val Leu Gln Asn Arg Arg
    370                 375                 380
Ala Leu Asp Leu Leu Thr Ala Lys Arg Gly Gly Thr Cys Leu Phe Leu
385                 390                 395                 400
Gly Glu Glu Arg Cys Tyr Tyr Val Asn Gln Ser Arg Ile Val Thr Glu
                405                 410                 415
Lys Val Lys Glu Ile Arg Asp Arg Ile Gln Cys Arg Ala Glu Glu Leu
            420                 425                 430
Gln Asn Thr Glu Arg Trp Gly Leu Leu Ser Gln Trp Met Pro Trp Val
```

435 440 445

Leu Pro Phe Leu Gly Pro Leu Ala Ala Leu Ile Leu Leu Leu Leu Phe
450 455 460

Gly Pro Cys Ile Phe Asn Leu Leu Val Lys Phe Val Ser Ser Arg Ile
465 470 475 480

Glu Ala Val Lys Leu Gln Met Val Leu Gln Met Glu Pro
485 490

(2) INFORMATION FOR SEQ ID NO: 119:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 32 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 119:

TCAAAATCGA AGAGCTTTAG ACTTGCTAAC CG 32

(2) INFORMATION FOR SEQ ID NO: 120:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1329 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 120:

TCAAAATCGA AGAGCTTTAG ACTTGCTAAC CGCCAAAAGA GGGGGAACCT GTTTATTTTT 60
AGGGGAAGAA TGCTGTTAGT ATGTTAATCA ATCTGGAATC ATTACTGAGA AAGTTAAAGA 120
AATTTGAGAT CGAATATAAT GTAGAGCAGA GGACCTTCAA AACACTGCAC CCTGGGGCCT 180
CCTCAGCCAA TGGATGCCCT GGACTCTCCC CTTCTTAGGA CCTCTAGCAG CTATAATATT 240
TTTACTCCTC TTTGGACCCT GTATCTTCAA CTTCCTTGTT AAGTTTGTCT CTTCCAGAAT 300
TGAAGCTGTA AAGCTACAAA TAGTTCTTCA AATGGAACCC CAGATGCAGT CCATGACTAA 360
AATCTACCGT GGACCCCTGG ACCGGCCTGC TAGACTATGC TCTGATGTTA ATGACATTGA 420
AGTCACCCCT CCCGAGGAAA TCTCAACTGC ACAACCCCTA CTACACTCCA ATTCAGTAGG 480
AAGCAGTTAG AGCAGTTGTC AGCCAACCTC CCCAACAGTA CTTGGGTTTT CCTGTTGAGA 540
GGGTGGACTG AGAGACAGGA CTAGCTGGAT TTCCTAGGCT GACTAAGAAT CCCNAAGCCT 600

```
ANCTGGGAAG GTGACCGCAT CCATCTTTAA ACATGGGGCT TGCAACTTAG CTCACACCCG  660
ACCAATCAGA GAGCTCACTA AAATGCTAAT CAGGCAAAAA CAGGAGGTAA AGCAATAGCC  720
AATCATCTAT TGCCTGAGAG CACAGCGGGA AGGACAAGGA TTGGGATATA AACTCAGGCA  780
TTCAAGCCAG CAACAGCAAC CCCCTTTGGG TCCCCTCCCA TTGTATGGGA GCTCTGTTTT  840
CACTCTATTT CACTCTATTA AATCATGCAA CTGCACTCTT CTGGTCCGTG TTTTTTATGG  900
CTCAAGCTGA GCTTTTGTTC GCCATCCACC ACTGCTGTTT GCCACCGTCA CAGACCCGCT  960
GCTGACTTCC ATCCCTTTGG ATCCAGCAGA GTGTCCACTG TGCTCCTGAT CCAGCGAGGT 1020
ACCCATTGCC ACTCCCGATC AGGCTAAAGG CTTGCCATTG TTCCTGCATG GCTAAGTGCC 1080
TGGGTTTGTC CTAATAGAAC TGAACACTGG TCACTGGGTT CCATGGTTCT CTTCCATGAC 1140
CCACGGCTTC TAATAGAGCT ATAACACTCA CCGCATGGCC CAAGATTCCA TTCCTTGGTA 1200
TCTGTGAGGC CAAGAACCCC AGGTCAGAGA ANGTGAGGCT TGCCACCATT TGGGAAGTGG 1260
CCCACTGCCA TTTTGGTAGC GGCCCACCAC CATCTTGGGA GCTGTGGGAG CAAGGATCCC 1320
CCAGTAACA                                                          1329
```

(2) INFORMATION FOR SEQ ID NO: 121:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 162 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 121:

```
Gln Asn Arg Arg Ala Leu Asp Leu Leu Thr Ala Lys Arg Gly Gly Thr
1               5                  10                  15
Cys Leu Phe Leu Gly Glu Glu Cys Cys Xaa Tyr Val Asn Gln Ser Gly
            20                  25                  30
Ile Ile Thr Glu Lys Val Lys Glu Ile Xaa Asp Arg Ile Xaa Cys Arg
        35                  40                  45
Ala Glu Asp Leu Gln Asn Thr Ala Pro Trp Gly Leu Leu Ser Gln Trp
    50                  55                  60
Met Pro Trp Thr Leu Pro Phe Leu Gly Pro Leu Ala Ala Ile Ile Phe
65                  70                  75                  80
Leu Leu Leu Phe Gly Pro Cys Ile Phe Asn Phe Leu Val Lys Phe Val
                85                  90                  95
Ser Ser Arg Ile Glu Ala Val Lys Leu Gln Ile Val Leu Gln Met Glu
            100                 105                 110
```

Pro Gln Met Gln Ser Met Thr Lys Ile Tyr Arg Gly Pro Leu Asp Arg
115 120 125
Pro Ala Arg Leu Cys Ser Asp Val Asn Asp Ile Glu Val Thr Pro Pro
130 135 140
Glu Glu Ile Ser Thr Ala Gln Pro Leu Leu His Ser Asn Ser Val Gly
145 150 155 160
Ser Ser

(2) INFORMATION FOR SEQ ID NO: 122:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 122:

GGCATTGATA GCACCCATCA G 21

(2) INFORMATION FOR SEQ ID NO: 123:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 123:

CATGTCACCA GGGTGGAATA G 21

(2) INFORMATION FOR SEQ ID NO: 124:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 124:

(2) INFORMATION FOR SEQ ID NO: 124:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 758 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 124:

```
GGCATTGATA GCACCCATCA GATGGCCAAA TCATTATTTA CTGGACCAGG CCTTTTCAAA   60
ACTATCAAGC AGATAGGGCC CGTGAAGCAT GCCAAAGAAA TAATCCCCTG CCTTATCGCC  120
ATGTTCCTTC AGGAGAACAA AGAACAGGCC ATTACCCAGG GGAAGACTGG CAACTAGATT  180
TTACCCACAT GGCCAAATGT CAGGGATTTC AGCATCTACT AGTCTGGGCA GATACTTTCA  240
CTGGTTGGGT GGAGTCTTCT CCTTGTAGGA CAGAAAAGAC CCAAGAGGTA ATAAAGGCAC  300
TAATGAAATA ATTCCCAGAT TTGGACTTCC CCCAGGATTA CAGGGTGACA ATGGCCCCGC  360
TTTCAAGGCT GCAGTAACCC AGGGAGTATC CCAGGTGTTA GGCATACAAT ATCACTTACA  420
CTGTGCCTGG AGGCCACAAT CCTCCAGAAA AGTCAAGAAA ATGAATGAAA CACTCAAAGA  480
TCTAAAAAAG CTAACCCAAG AAACCCACAT TGCATGACCT GTTCTGTTGC CTATAACCTT  540
ACTAAGAATC CATAACTATC CCCCAAAAAG CAGGACTTAG CCCATACGAG ATGCTATATG  600
GATGGCCTTT CCTAACCAAT GACCTTGTGC TTGACTGAGA AATGGCCAAC TTAGTTGCAG  660
ACATCACCTC CTTAGCCAAA TATCAACAAG TTCTTAAAAC ATCACAGGGA ACCTGTCCCC  720
GAGAGGAGGG AAAGGAACTA TTCCACCCTG GTGACATG                          758
```

(2) INFORMATION FOR SEQ ID NO: 126:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 126:

CGGACATCCA AAGTGATGGG AAACG 25

(2) INFORMATION FOR SEQ ID NO: 127:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 127:

GGACAGGAAA GTAAGACTGA GAAGGC 26

(2) INFORMATION FOR SEQ ID NO: 128:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 128:

CCTAGAACGT ATTCTGGAGA ATTGGG 26

(2) INFORMATION FOR SEQ ID NO: 129:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 129:

TGGCTCTCAA TGGTCAAACA TACCCG 26

(2) INFORMATION FOR SEQ ID NO: 130:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1511 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 130:

CCTAGAACGT ATTCTGGAGA ATTGGGACCA ATGTGACACT CAGACGCTAA GAAAGAAACG 60

```
ATTTATATTC TTCTGCAGTA CCGCCTGGCC ACAATATCCT CTTCAAGGGA GAGAAACCTG  120
GCTTCCTGAG GGAAGTATAA ATTATAACAT CATCTTACAG CTAGACCTCT TCTGTAGAAA  180
GGAGGGCAAA TGGAGTGAAG TGCCATATGT GCAAACTTTC TTTTCATTAA GAGACAACTC  240
ACAATTATGT AAAAAGTGTG GTTTATGCCC TACAGGAAGC CCTCAGAGTC CACCTCCCTA  300
CCCCAGCGTC CCCTCCCCGA CTCCTTCCTC AACTAATAAG GACCCCCCTT TAACCCAAAC  360
GGTCCAAAAG GAGATAGACA AAGGGGTAAA CAATGAACCA AAGAGTGCCA ATATTCCCCG  420
ATTATGCCCC CTCCAAGCAG TGAGAGGAGG AGAATTCGGC CCAGCCAGAG TGCCTGTACC  480
TTTTTCTCTC TCAGACTTAA AGCAAATTAA AATAGACCTA GGTAAATTCT CAGATAACCC  540
TGACGGCTAT ATTGATGTTT TACAAGGGTT AGGACAATCC TTTGATCTGA CATGGAGAGA  600
TATAATGTTA CTACTAAATC AGACACTAAC CCCAAATGAG AGAAGTGCCG CTGTAACTGC  660
AGCCCGAGAG TTTGGCGATC TTTGGTATCT CAGTCAGGCC AACAATAGGA TGACAACAGA  720
GGAAAGAACA ACTCCCACAG GCCAGCAGGC AGTTCCCAGT GTAGACCCTC ATTGGGACAC  780
AGAATCAGAA CATGGAGATT GGTGCCACAA ACATTTGCTA ACTTGCGTGC TAGAAGGACT  840
GAGGAAAACT AGGAAGAAGC CTATGAATTA CTCAATGATG TCCACTATAA CACAGGGAAA  900
GGAAGAAAAT CTTACTGCTT TTCTGGACAG ACTAAGGGAG GCATTGAGGA AGCATACCTC  960
CCTGTCACCT GACTCTATTG AAGGCCAACT AATCTTAAAG GATAAGTTTA TCACTCAGTC 1020
AGCTGCAGAC ATTAGAAAAA ACTTCAAAAG TCTGCCTTAG GCCCGGAGCA GAACTTAGAA 1080
ACCCTATTTA ACTTGGCATC CTCAGTTTTT TATAATAGAG ATCAGGAGGA GCAGGCGAAA 1140
CGGGACAAAC GGGATAAAAA AAAAAGGGGG GGTCCACTAC TTTAGTCATG GCCCTCAGGC 1200
AAGCAGACTT TGGAGGCTCT GCAAAAGGGA AAAGCTGGGC AAATCAAATG CCTAATAGGG 1260
CTGGCTTCCA GTGCGGTCTA CAAGGACACT TTAAAAAAGA TTATCCAAGT AGAAATAAGC 1320
CGCCCCCTTG TCCATGCCCC TTACGTCAAG GGAATCACTG GAAGGCCCAC TGCCCCAGGG 1380
GATGAAGATA CTCTGAGTCA GAAGCCATTA ACCAGATGAT CCAGCAGCAG GACTGAGGGT 1440
GCCCGGGGCG AGCGCCAGCC CATGCCATCA CCCTCACAGA GCCCCGGGTA TGTTTGACCA 1500
TTGAGAGCCA A                                                      1511
```

(2) INFORMATION FOR SEQ ID NO: 131:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 352 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 131:

```
Leu Glu Arg Ile Leu Glu Asn Trp Asp Gln Cys Asp Thr Gln Thr Leu
 1               5                  10                  15
```

```
Arg Lys Lys Arg Phe Ile Phe Phe Cys Ser Thr Ala Trp Pro Gln Tyr
            20                  25                  30
Pro Leu Gln Gly Arg Glu Thr Trp Leu Pro Glu Gly Ser Ile Asn Tyr
        35                  40                  45
Asn Ile Ile Leu Gln Leu Asp Leu Phe Cys Arg Lys Glu Gly Lys Trp
    50                  55                  60
Ser Glu Val Pro Tyr Val Gln Thr Phe Phe Ser Leu Arg Asp Asn Ser
65                  70                  75                  80
Gln Leu Cys Lys Lys Cys Gly Leu Cys Pro Thr Gly Ser Pro Gln Ser
                85                  90                  95
Pro Pro Pro Tyr Pro Ser Val Pro Ser Pro Thr Pro Ser Ser Thr Asn
            100                 105                 110
Lys Asp Pro Pro Leu Thr Gln Thr Val Gln Lys Glu Ile Asp Lys Gly
        115                 120                 125
Val Asn Asn Glu Pro Lys Ser Ala Asn Ile Pro Arg Leu Cys Pro Leu
    130                 135                 140
Gln Ala Val Arg Gly Gly Glu Phe Gly Pro Ala Arg Val Pro Val Pro
145                 150                 155                 160
Phe Ser Leu Ser Asp Leu Lys Gln Ile Lys Ile Asp Leu Gly Lys Phe
                165                 170                 175
Ser Asp Asn Pro Asp Gly Tyr Ile Asp Val Leu Gln Gly Leu Gly Gln
            180                 185                 190
Ser Phe Asp Leu Thr Trp Arg Asp Ile Met Leu Leu Leu Asn Gln Thr
        195                 200                 205
Leu Thr Pro Asn Glu Arg Ser Ala Ala Val Thr Ala Ala Arg Glu Phe
    210                 215                 220
Gly Asp Leu Trp Tyr Leu Ser Gln Ala Asn Asn Arg Met Thr Thr Glu
225                 230                 235                 240
Glu Arg Thr Thr Pro Thr Gly Gln Gln Ala Val Pro Ser Val Asp Pro
                245                 250                 255
His Trp Asp Thr Glu Ser Glu His Gly Asp Trp Cys His Lys His Leu
            260                 265                 270
Leu Thr Cys Val Leu Glu Gly Leu Arg Lys Thr Arg Lys Lys Pro Met
        275                 280                 285
Asn Tyr Ser Met Met Ser Thr Ile Thr Gln Gly Lys Glu Glu Asn Leu
    290                 295                 300
```

```
1               5                  10                  15
Arg Gly Ser His Met Ala Ser Met Thr Gly Gly Gln Gln Met Gly Arg
            20                  25                  30
Ile Leu Glu Arg Ile Leu Glu Asn Trp Asp Gln Cys Asp Thr Gln Thr
        35                  40                  45
Leu Arg Lys Lys Arg Phe Ile Phe Phe Cys Ser Thr Ala Trp Pro Gln
    50                  55                  60
Tyr Pro Leu Gln Gly Arg Glu Thr Trp Leu Pro Glu Gly Ser Ile Asn
65                  70                  75                  80
Tyr Asn Ile Ile Leu Gln Leu Asp Leu Phe Cys Arg Lys Glu Gly Lys
                85                  90                  95
Trp Ser Glu Val Pro Tyr Val Gln Thr Phe Phe Ser Leu Arg Asp Asn
            100                 105                 110
Ser Gln Leu Cys Lys Lys Cys Gly Leu Cys Pro Thr Gly Ser Pro Gln
        115                 120                 125
Ser Pro Pro Pro Tyr Pro Ser Val Pro Ser Pro Thr Pro Ser Ser Thr
    130                 135                 140
Asn Lys Asp Pro Pro Leu Thr Gln Thr Val Gln Lys Glu Ile Asp Lys
145                 150                 155                 160
Gly Val Asn Asn Glu Pro Lys Ser Ala Asn Ile Pro Arg Leu Cys Pro
                165                 170                 175
Leu Gln Ala Val Arg Gly Gly Glu Phe Gly Pro Ala Arg Val Pro Val
            180                 185                 190
Pro Phe Ser Leu Ser Asp Leu Lys Gln Ile Lys Ile Asp Leu Gly Lys
        195                 200                 205
Phe Ser Asp Asn Pro Asp Gly Tyr Ile Asp Val Leu Gln Gly Leu Gly
    210                 215                 220
Gln Ser Phe Asp Leu Thr Trp Arg Asp Ile Met Leu Leu Leu Asn Gln
225                 230                 235                 240
Thr Leu Thr Pro Asn Glu Arg Ser Ala Ala Val Thr Ala Ala Arg Glu
                245                 250                 255
Phe Gly Asp Leu Trp Tyr Leu Ser Gln Ala Asn Asn Arg Met Thr Thr
            260                 265                 270
Glu Glu Arg Thr Thr Pro Thr Gly Gln Gln Ala Val Pro Ser Val Asp
        275                 280                 285
Pro His Trp Asp Thr Glu Ser Glu His Gly Asp Trp Cys His Lys His
```

290 295 300

Leu Leu Thr Cys Val Leu Glu Gly Leu Arg Lys Thr Arg Lys Lys Pro
305 310 315 320
Met Asn Tyr Ser Met Met Ser Thr Ile Thr Gln Gly Lys Glu Glu Asn
325 330 335
Leu Thr Ala Phe Leu Asp Arg Leu Arg Glu Ala Leu Arg Lys His Thr
340 345 350
Ser Leu Ser Pro Asp Ser Ile Glu Gly Gln Leu Ile Leu Lys Asp Lys
355 360 365
Phe Ile Thr Gln Ser Ala Ala Asp Ile Arg Lys Asn Phe Lys Ser Leu
370 375 380
Pro Lys Leu Ala Ala Ala Leu Glu His His His His His His
385 390 395

(2) INFORMATION FOR SEQ ID NO: 137:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 378 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 137:

Met Ala Ser Met Thr Gly Gly Gln Gln Met Gly Arg Ile Leu Glu Arg
1 5 10 15
Ile Leu Glu Asn Trp Asp Gln Cys Asp Thr Gln Thr Leu Arg Lys Lys
20 25 30
Arg Phe Ile Phe Phe Cys Ser Thr Ala Trp Pro Gln Tyr Pro Leu Gln
35 40 45
Gly Arg Glu Thr Trp Leu Pro Glu Gly Ser Ile Asn Tyr Asn Ile Ile
50 55 60
Leu Gln Leu Asp Leu Phe Cys Arg Lys Glu Gly Lys Trp Ser Glu Val
65 70 75 80
Pro Tyr Val Gln Thr Phe Phe Ser Leu Arg Asp Asn Ser Gln Leu Cys
85 90 95
Lys Lys Cys Gly Leu Cys Pro Thr Gly Ser Pro Gln Ser Pro Pro Pro
100 105 110

Tyr Pro Ser Val Pro Ser Pro Thr Pro Ser Ser Thr Asn Lys Asp Pro
115 120 125
Pro Leu Thr Gln Thr Val Gln Lys Glu Ile Asp Lys Gly Val Asn Asn
130 135 140
Glu Pro Lys Ser Ala Asn Ile Pro Arg Leu Cys Pro Leu Gln Ala Val
145 150 155 160
Arg Gly Gly Glu Phe Gly Pro Ala Arg Val Pro Val Pro Phe Ser Leu
165 170 175
Ser Asp Leu Lys Gln Ile Lys Ile Asp Leu Gly Lys Phe Ser Asp Asn
180 185 190
Pro Asp Gly Tyr Ile Asp Val Leu Gln Gly Leu Gly Gln Ser Phe Asp
195 200 205
Leu Thr Trp Arg Asp Ile Met Leu Leu Leu Asn Gln Thr Leu Thr Pro
210 215 220
Asn Glu Arg Ser Ala Ala Val Thr Ala Ala Arg Glu Phe Gly Asp Leu
225 230 235 240
Trp Tyr Leu Ser Gln Ala Asn Asn Arg Met Thr Thr Glu Glu Arg Thr
245 250 255
Thr Pro Thr Gly Gln Gln Ala Val Pro Ser Val Asp Pro His Trp Asp
260 265 270
Thr Glu Ser Glu His Gly Asp Trp Cys His Lys His Leu Leu Thr Cys
275 280 285
Val Leu Glu Gly Leu Arg Lys Thr Arg Lys Lys Pro Met Asn Tyr Ser
290 295 300
Met Met Ser Thr Ile Thr Gln Gly Lys Glu Glu Asn Leu Thr Ala Phe
305 310 315 320
Leu Asp Arg Leu Arg Glu Ala Leu Arg Lys His Thr Ser Leu Ser Pro
325 330 335
Asp Ser Ile Glu Gly Gln Leu Ile Leu Lys Asp Lys Phe Ile Thr Gln
340 345 350
Ser Ala Ala Asp Ile Arg Lys Asn Phe Lys Ser Leu Pro Lys Leu Ala
355 360 365
Ala Ala Leu Glu His His His His His His
370 375

(2) INFORMATION FOR SEQ ID NO: 138:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 138:

CTTGGAGGGT GCATAACCAG GGAAT 25

(2) INFORMATION FOR SEQ ID NO: 139:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 139:

TGTCCGCTGT GCTCCTGATC 20

(2) INFORMATION FOR SEQ ID NO: 140:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 140:

CTATGTCCTT TTGGACTGTT TGGGT 25

(2) INFORMATION FOR SEQ ID NO: 141:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 764 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 141:

TGTCCGCTGT GCTCCTGATC CAGCACAGGC GCCCATTGCC TCTCCCAATT GGGCTAAAGG 60
CTTGCCATTG TTCCTGCACA GCTAAGTGCC TGGGTTCATC CTAATCGAGC TGAACACTAG 120
TCACTGGGTT CCACGGTTCT CTTCCATGAC CCATGGCTTC TAATAGAGCT ATAACACTCA 180
CTGCATGGTC CAAGATTCCA TTCCTTGGAA TCCGTGAGAC CAAGAACCCC AGGTCAGAGA 240
ACACAAGGCT TGCCACCATG TTGGAAGCAG CCCACCACCA TTTTGGAAGC AGCCCGCCAC 300
TATCTTGGGA GCTCTGGGAG CAAGGACCCC AGGTAACAAT TTGGTGACCA CGAAGGGACC 360
TGAATCCGCA ACCATGAAGG GATCTCCAAA GCAATTGGAA ATGTTCCTCC CAAGGCAAAA 420
ATGCCCCTAA GATGTATTCT GGAGAATTGG GACCAATTTG ACCCTCAGAC AGTAAGAAAA 480
AAATGACTTA TATTCTTCTG CAGTACCGCC CTGGCCACGA TATCCTCTTC AAGGGGGAGA 540
AACCTGGCCT CCTGAGGGAA GTATAAATTA TAACACCATC TTACAGCTAG ACCTGTTTTC 600
TAGAAAAGGA GGCAAATGGA GTGAAGTGCC ATATTTACAA ACTTTCTTTT CATTAAAAGA 660
CAACTCGCAA TTATGTTAAC AGTGTGATTT GTGTTCCTAC ACGGAAGCCC TCAGATTCTA 720
CTCCCCACCC CCGGCATCTC CCCTGAATCC CTCCCCAACT TATT 764

(2) INFORMATION FOR SEQ ID NO: 142:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 800 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 142:

TGTCCGCTGT GCTCCTGATC CAGCACAGGC GCCCATTGCC TCTCCCAATT GGGCTAAAGG 60
CTTGCCATTG TTCCTGCACA GCTAAGTGCC TGGGTTCATC CTAATCGAGC TGAACACTAG 120
TCACTGGGTT CCACGGTTCT CTTCCATGAC CCATGGCTTC TAATAGAGCT ATAACACTCA 180
CTGCATGGTC CAAGATTCCA TTCCTTGGAA TCCGTGAGAC CAAGAACCCC AGGTCAGAGA 240
ACACAAGGCT TGCCACCATG TTGGAAGCAG CCCACCACCA TTTTGGAAGC GGCCCGCCAC 300
TATCTTGGGA GCTCTGGGAG CAAGGACCCC CAGGTAACAA TTTGGTGACC ACGAAGGGAC 360
CTGAATCCGC AACCATGAAG GGATCTCCAA AGCAATTGGA AATGTTCCTC CCAAGGCAAA 420
AATGCCCCTA AGATGTATTC TGGAGAATTG GGACCAATCT GACCCTCAGA CAGTAAGAAA 480
AAAAATGACT TATATTCTTC TGCAGTACCG CCTGGCCACG GATATCCTCT TCAAGGGGGA 540
GAAACCTGGC CTCCTGAGGG AAGTATAAAT TATAACACCA TCTTACAGCT AGACCTGTTT 600
TGTAGAAAAG GAGGCAAATG GAGTGAAGTG CCATATTTAC AAACTTTCTT TTCATTAAAA 660
GACAACTCGC AATTATGTAA ACAGTGTGAT TTGTGTCCTA CAGGAAGCCC TCAGATCTAC 720
CTCCCTACCC CGGCATCTCC CTGACTCCTT CCCCAACTAA TAAGGACCCA CTTCAGCCCA 780
AACAGTCCAA AAGGACATAG 800